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TRADITION AND PROGRESS IN MEDICINE*

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IT is a very real privilege for the members of the American College of Physicians to hold their thirty-eighth annual session in Boston where the traditions of medicine are so strong and where the progress of medicine is evident on every hand. We all join in paying tribute to our distinguished Boston predecessors who so masterfully advanced our knowledge—George Minot, Francis Peabody, our beloved Reginald Fitz and his father before him, James Jackson, Benjamin Waterhouse, Zabdiel Boylston, the several generations of remarkable Warrens, and many others down to the present time. Slowly over three centuries these men of science built the splendid traditions of medicine in Boston—traditions linking us with the treasured heritage of physicians all over the world.

This heritage was particularly dear to the heart of our past president, Dr. George Strong, whose untimely death on February 26 we deeply mourn. It is not possible for me to enumerate the many contributions of Dr. Strong to the life of the American College of Physicians, but he was a powerful, constructive force. We shall sorely miss his strong, friendly personality, his wise counsel and his inspiring, energetic leadership.

Dr. Strong was intensely interested in the coöperation of the American College of Physicians with the Royal Colleges of Physicians of London and Australasia. Last year in Los Angeles, he traced the history of the Royal College of Physicians of London. The Royal College represents the great endowment of British medicine and brings to mind familiar names from Sir Thomas Lewis and Sir James MacKenzie to Thomas Sydenham, William Harvey, and Thomas Linacre who, in 1518, founded the Royal College. We are happy to have with us tonight its representative in the person of the

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Right Honorable, the Lord Cohen of Birkenhead. We also welcome Dr. Edward Sayers, president of the Royal Australasian College of Physicians.

Proud as we are of our English speaking inheritance, we are also grateful for the contributions made by other nations. The beginning of the bacteriologic era, and, in a sense, the beginning of modern medicine, can be dated to the French chemist, Louis Pasteur. His compatriots of the French school included the physiologist Claude Bernard, the clinicians Laennec, Pierre Louis, Charcot and many others. To the German speaking peoples we are particularly indebted as we recall among many, the names of Virchow, Koch, Ludwig, Roentgen, von Helmholtz and Paul Ehrlich. The trail of our inheritance from the past grows dim as we enter the Dark Ages, but Rabbi Moses Maimonides with Rhazes, Avicenna and others of the Arabian school guide us back to Galen and Hippocrates; beyond them the trail is lost in the unrecorded history of the beginnings of civilization. As one looks back over the centuries, it is clear that knowledge has been added slowly, step by step; progress has been the continuing tradition of medicine.

The three phases into which medicine has always been divisible are teaching, research and practice. In these words, one can summarize all of our labors, our mistakes, our achievements, and our ambitions. The maintenance and advance of the highest possible standards constitute the first stated objective of the American College of Physicians. My chief thought this evening, however, is to emphasize the rôle of investigation and to suggest that its light must illumine both teaching and practice. Without research, medicine is fettered with traditions that bind.

Medical education, as we now understand the term, is relatively recent in its development in North America. The University of Pennsylvania founded a medical school in 1765. King's College of Physicians and Surgeons of New York, later to become the Medical School of Columbia University, was established in 1768. The Medical Institution of Harvard, later Harvard Medical School, appeared in 1783, the same year as Transylvania Medical College of Lexington, Kentucky. The faculties of these schools consisted of high grade practitioners who gave courses of lectures to supplement the apprenticeship training, or so-called "reading," of medicine customary at that time. In the next hundred years almost innumerable proprietary schools were established to give didactic lectures to everyone who registered. The development of a graded four year curriculum came slowly and was not complete until the very end of the nineteenth century. The elimination of the inferior proprietary schools with the general incorporation of the surviving schools into the Universities is a phenomenon occurring almost entirely in the past half century. The resultant integration of the medical curriculum into the intellectual and scientific life of the University is the most significant single development in the history of American medical education.

In the wake of this dramatic transformation in the undergraduate field,

there followed an equally dramatic and equally profound transformation in the medical training after graduation. It began with the creation of the hospital internship. An attempt by certain schools in the early nineteen hundreds to incorporate the internship into the undergraduate curriculum failed. The state examining boards, however, quick to appreciate the training value of the internship, made it a general requirement for licensure. Within a few years the hospital programs were extended to include residencies in the various specialties.

It is somewhat difficult to separate specialization and residency training. The residencies preparing men for the practice of specialties clearly developed before the establishment of the Boards. However, the programs received a terrific stimulus from the Boards, the number of residencies increasing ten-fold between 1934 and 1954. It is estimated that 25% of the physicians now in practice are Board Certified Specialists and that 74% of the medical graduates since 1945 have limited themselves to a specialty. There is every reason to think that the tremendous surge toward specialization will continue.

Where does research enter the educational picture? The beginnings of medicine and, in a sense, of research in medicine, like the beginnings of all science, are hidden in the mists of antiquity. We can guess that man first tried to treat his various afflictions by trial and error influenced by superstition. At least by the time of Hippocrates there were attempts to classify disease and to understand it. Galen and later Vesalius began to dissect cadavers. With Francis Bacon the experimental method was introduced into natural science and the planned experiment came to the aid of the older methods of observation, trial and error. Progress was slow. The true flowering of science has occurred in the past hundred years. The American Foundation under the leadership of Miss Esther Everett Lape has published a splendid analysis of the present status of medical research. Miss Lape first warns that "In a world in which the very word research has been debauched by application to every type of zealous noncreative activity from that of a school boy looking up a word in a dictionary to that of the research squad of an advertising company endeavoring to find out if there is a better market for poor candy in beautiful boxes or for good candy in plain boxes, the wary will avoid generalizations." She then points out that "in medical and biological research there are many levels. Just as artists are few but practitioners and lovers of the arts many, so among investigators in biology and medicine and other fields of science, there are few carriers of the flame but many who either as individuals or members of 'teams' make a serious and disinterested contribution to research."

With respect to the rôle of research in undergraduate education, Miss Lape notes that "The objective of the undergraduate curriculum is to teach the student how to continue his education. To the degree to which research has been inherent in his teachers and his teaching (emphasizing the unknown

and the hypothetical, as well as the known) it becomes basic in the young physician's work. The poor practitioners of the present are often the products of teaching that has been concerned with the dogma of the past rather than with the fluid truth of the present. It is through contact with research that the medical student learns that the present fixations are likely to be less than ultimate truths; it is through research that the student or teacher or practitioner maintains a lively realization of the rapidly moving boundaries of medical science and of the degree to which the validity of his work depends upon understanding that, in the present state of the biological sciences, no part of his knowledge is static." Miss Lape thus concludes that research should be an integral part of medical education. The greatest obstacle is lack of time for both students and teachers. In the majority of schools the routine course work is so heavy that there is no time for research. In one institution, however, the faculty and students gather at the end of the senior year to hear a program of selected papers presented by the students reporting their own investigations; the success of the undertaking has been highly stimulating to the faculty.

After graduation the young physician enters his internship, where he receives a rich, indeed an invaluable, clinical experience, often in an atmosphere of research, but rarely with an opportunity for him to participate. He then proceeds to the residency, a hospital oriented program even in the teaching institutions, devoting three years to clinical work with autopsy and other conferences—the routine of looking back, but with little or no opportunity to look forward or even sidewise! It seems to me that the rôle of investigation in the program of the residency, as well as in undergraduate education, should receive greater recognition. The longer a young physician defers his entrance into research, the more difficult it becomes. The opportunities for research in all hospitals should be increased and extended. In non-university hospitals, the present trend toward full time senior positions should favor this development. In some university institutions an entire year is now set aside for study and experiment by the resident; in others arrangements can be made for creative work on a part time basis for two or more of the residency years. The financial support available for such research from private, industrial and governmental sources now exceeds our wildest dreams of 20 years ago. The intellectual caliber of the resident's research should be comparable to that of candidates for higher degrees in other fields of science, and, ideally, the university should formally recognize the residency as a part of its academic program. The suggestion of advanced degrees for research done during this period may seem visionary, but it has precedent and it is completely in accord with the academic tradition.

The rôle of the American College of Physicians as a catalyst in the improvement of the residency has yet to be defined. The American Board of Internal Medicine concerns itself primarily with the clinical content of the program. The American College of Physicians, by its requirement of Board

Certification for advancement to full fellowship, has accepted this emphasis, and it has done little to promote or encourage research in this phase of the life of the young physician.

And what about research after completion of the residency? This depends essentially upon the maintenance of an inquiring mind in the practice of medicine through life. The clinician, unskilled in the technics of the laboratory, sometimes concludes that he has no opportunity to do research. This is untrue; opportunities are at every hand; in medicine as elsewhere, "gold is where you find it." The clinical problems to which men in practice can contribute are almost endless. Mechanisms of disease and of reaction cry continuously for explanation. The biochemistry of medicine is in its infancy. Instruments and methods are increasingly available everywhere. In almost every hospital in the country there is a need for better records, for better analyses of what is being done, for registries and follow-up programs to determine with greater precision the natural course of the disease, the effect of therapy, the survival and recurrence rates, and so on.

The clinician, as he looks with some envy at the beautiful, peaceful laboratories of his colleagues in the basic sciences should recall the lowly origin of many of the most important medical discoveries. Although Jenner was the first to demonstrate the potentialities of vaccination for smallpox, the procedure originated in some pre-historic age devoid of gleaming laboratories and scientific gadgets. Withering listened to the tales of an old woman's secret remedy for dropsy, identified foxglove, and thus discovered digitalis. Many years later, Vogl noted that nurses, uselessly charting the urinary output of patients, regularly recorded an increase after the administration of an organic mercurial to syphilitic patients; thus was the diuretic effect of the mercurial drugs discovered. Sir James Mackenzie studied the patients who came to him and wrote his classic treatise on heart disease. Lord Lister grasped the significance of the discoveries of Pasteur, instituted anti-sepsis in the operating room and founded modern aseptic surgery. George Minot and William Murphy here in Boston fed liver to patients with pernicious anemia, made a completely new discovery recorded in case reports, won the Nobel Prize, and added years to the lives of untold numbers of men and women. The methods used by these men were all simple but *ideas* were present, ideas arising in prepared minds. In such ways, with persistence and perseverance, the clinician day by day can help to extend our knowledge and to push slowly back the borders of the unknown.

The profound changes in the practice of medicine in the past century have been the result of research. The gradual extension of public health programs and the rise of preventive medicine have decreased the death rate and increased life expectancy throughout the civilized world. The tremendous impact of these phenomena upon the population pressures is beginning to be felt. The advance of science has brought us problems for the solution of which there is neither tradition nor precedent, and which, faced by man

for the first time in the twentieth century, have their import for the practice of medicine.

But to return to the triad of teaching, research and practice, it is clear that they constitute a unity, the three fold way of a physician. Research illumines his life, inspires his teaching, and clarifies his practice. The drive of curiosity to learn, to know, to measure, to investigate, to explore the unknown, arises in every one. Fortunate, indeed, is he who has the opportunity to fan the flame of the investigative spirit; it is one of life's greatest blessings. Teaching and practice each have their rewards in the life of a physician, but research is the golden link. Research dissolves the outworn traditions of the past and enables medicine to progress into the future.

My plea tonight is that both the undergraduate curriculum and the residency program should provide, first, training in the methods of research and, second, opportunity for investigation so that the intellectual habit of scientific inquiry may become a way of life for all physicians. The medical schools are responsible for the undergraduate phase. Who is to accept responsibility for the graduate phase? The educational content and the opportunity for investigation in the residency would be improved if it could be given status in the framework of the university; unfortunately, at the present time, the universities lack the manpower and the orientation necessary to bring this about. Perhaps the American College of Physicians should rise to the challenge of the opportunity; in a sense, a beginning already has been made through the Residency Review Committee, the only committee in American Medicine concerning itself with residency training in Internal Medicine. The work of this committee is most important. The residents of today are the leaders of tomorrow. Devotion to the spirit of scientific inquiry may lead many of our residents on to new discoveries; certainly it will make them better teachers and better practitioners of medicine. It is to be hoped that the same spirit will continue with them through life. Acceptance of the challenge of the unknown is the tradition of medicine.

You young men and women admitted into the Fellowship of the College tonight have demonstrated outstanding clinical ability. You are competent to practice internal medicine. You are competent to teach by precept and by example. You are competent to carry on research and to maintain the highest standards of clinical investigation. Into your hands we pass the traditions of medicine inherited by us from a long line of distinguished men and women; on your shoulders we place responsibility for the further progress of medicine. We have complete confidence in you and in your ability to pass on to the next generation this bequest enriched by the contribution you will have made.

CHARACTERISTICS OF THE INDIVIDUAL AS GUIDEPOSTS TO THE PREVENTION OF HEART DISEASE*

By Caroline Bedell Thomas, F.A.C.P., *Baltimore, Maryland*

It is a great honor to be asked to give the James D. Bruce Memorial Lecture in Preventive Medicine today. To be thus chosen is profoundly gratifying, and I should like to express my deepest appreciation to the Board of Regents of The American College of Physicians for this distinction, which I share with Dr. Alvin Coburn. It is worthy of note that this is the first Bruce Memorial Lectureship to be devoted to problems concerned with the prevention of heart disease. At the inception of the Bruce Lectures in 1948, the late Brigadier General James Stevens Simmons pointed out the need for preventive measures for the chronic degenerative diseases, with heart disease heading the list as the most important cause of death.[1] "Failure to control these diseases," he said, "reflects the general ignorance concerning the underlying causes, and emphasizes the need for basic research aimed at the discovery of better methods of prevention. . . ."

Steps in that direction, however, were already under way. Twenty years ago this April, the first season's trial of chemoprophylaxis directed toward the prevention of rheumatic fever and rheumatic heart disease was almost complete.[2] Although the number of persons studied was small, the results were encouraging. It is particularly rewarding to trace the growth of that single idea from its simple beginnings, through a period of opposition and controversy, to its present use on a wide scale. It is now recognized that through the protection of sulfonamide or penicillin prophylaxis, over 90% of major rheumatic episodes can be prevented. The effectiveness of this measure in decreasing recurrences of rheumatic fever and subsequent rheumatic heart disease gives promise that other forms of heart disease may yield to the preventive approach in similar fashion.

Before proceeding, I should like to pay tribute to Dr. Perrin H. Long for the part he played in assisting the launching of our program directed toward preventing recurrent attacks of rheumatic fever. In September, 1936, he brought the news from a London conference of the discovery that

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Support for the long-term study has come from the following sources: Research Grant 215, the United States Public Health Service, Federal Security Agency; funds made available for research by Abbott Laboratories, Eli Lilly & Company, Lederle Laboratories Division American Cyanamid Company, Parke, Davis & Company and the Upjohn Company; Research Contract V1001M-2768, Veterans Administration; Research Grant H-1891, National Heart Institute; the Tobacco Industry Research Committee.

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sulfanilamide was effective not only in curing beta hemolytic streptococcal infections, but, in experimental animals, in preventing them as well.[3-5] It seemed to me that here was the very substance we had been waiting for to prevent rheumatic fever. In his "Factor of Infection in the Rheumatic State," Coburn had brought forward several types of evidence indicating that beta hemolytic streptococcal infections usually precede rheumatic recurrences.[6] However, up to that time the prophylactic effect of sulfanilamide on any type of infection had been demonstrated only in mice. When I asked Dr. Long what dose of sulfanilamide might be used in human prophylaxis, particularly adolescents and young adults, he thought a moment, and then said, "I think a gram a day would be about right." Accordingly, we adopted this dosage. Twenty years later, a gram a day is the exact amount of sulfanilamide or sulfadiazine which provides complete protection![7]

The idea that rheumatic heart disease might be prevented by daily doses of sulfanilamide rested upon the synthesis of four concepts:

1. Individuals susceptible to acute rheumatic fever tend to have recurrent attacks.
2. Heart disease develops in many persons suffering from recurrences of rheumatic fever.
3. Episodes of rheumatic fever are usually preceded by beta hemolytic streptococcal infections.
4. Sulfanilamide in small doses prevents beta hemolytic streptococcal infections.

At that time, only the first two concepts were generally accepted; the third was still controversial and needed further clinical confirmation. Finally, the idea of preventing human infection by small daily doses of a drug was new and awaited clinical trial. The fact that rheumatic subjects tend to have recurrences made it possible to test the new hypothesis upon a group with a high attack rate of rheumatic fever—individuals whose susceptibility had already been demonstrated by at least one attack.[2, 8-10] If no such guidepost to identify a susceptible population had existed, efforts to prove the value of sulfanilamide in the prevention of rheumatic fever would have been much delayed, if not completely defeated, because of the infrequent occurrence of rheumatic fever in the general population.

Identification of susceptible groups for the purpose of testing preventive measures is also important in other types of heart disease. Today, our hopes are turning toward the prevention of coronary and hypertensive heart disease in the not too distant future. We are well aware that these two closely related disorders are more frequent and more disastrous in the United States than anywhere else in the world. Significant modification of some of the factors which contribute both to the American way of life and to the high incidence of heart disease now appears possible—whether by means of new medicines or hormones, by altered habits of diet, exercise or smoking, by reduction of "stress" or change in psychologic attitudes, by combinations

of these measures, or by some entirely new approach. Unlike rheumatic fever, the first attack of coronary occlusion is all too often fatal, and irreversible vascular damage may attend the clinical appearance of hypertension. Successful prevention of these diseases depends upon the selection of groups of susceptible individuals *before* the attack has occurred.

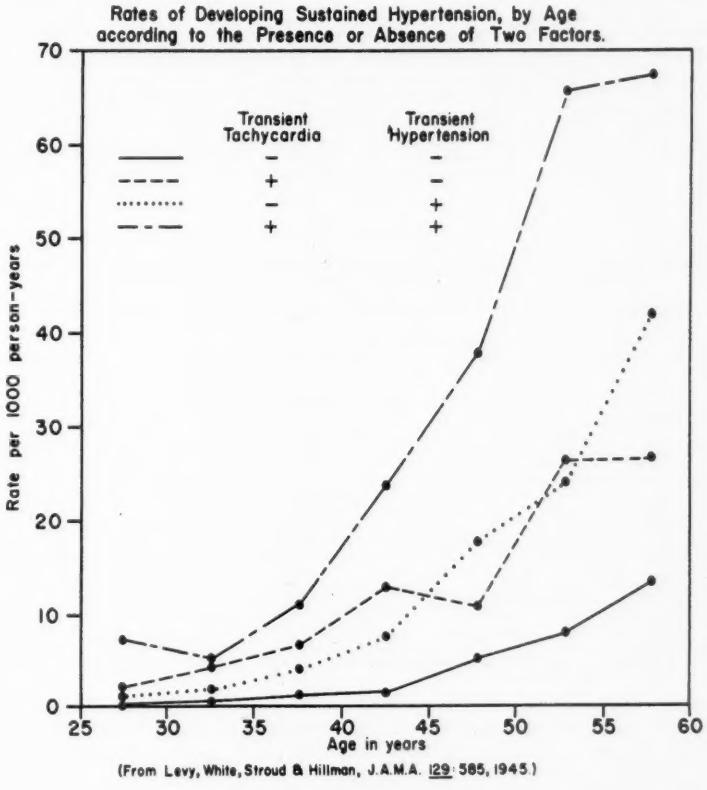
Rates of Developing Sustained Hypertension, by Age according to the Presence or Absence of Two Factors.
Transient Tachycardia
Transient Hypertension
Rate per 1000 person-years
Age in years
(From Levy, White, Stroud & Hillman, J.A.M.A. 129: 585, 1945.)

FIG. 1.

What are the characteristics now known to precede hypertension and coronary heart disease, either singly or combined, which may serve as guideposts to the selection of susceptible individuals? The factor of vascular hyperreactivity has long been studied by Hines and his associates.[11, 12] They discovered that most persons with essential hypertension react to a standardized cold pressor test with excessive rises of blood pressure. Some individuals with normal blood pressure also react excessively. They postulated that among these "normal hyperreactors" instances of essential hyper-

tension would appear. This hypothesis has now been verified. Partial follow-up studies after 15 years indicate that many more cases of hypertension develop among persons who were originally "normal hyperreactors" to the cold pressor test than among two less reactive groups.[13, 14] Circulatory hyperreactivity, then, is a forerunner of hypertension.

Of special importance are the studies of Levy, White, Stroud and Hillman, who showed transitory elevation of blood pressure and of heart rate to be precursors of later sustained hypertension, as well as of disability and death from cardiovascular renal disease, including hypertension and coronary heart disease. The annual physical examinations of 22,741 army officers were searched for instances of elevation of blood pressure above 150 mm. systolic or 90 mm. diastolic pressure, with subsequent readings below these levels.[15] This circumstance they called "transient hypertension." In all

TABLE 1

Ratio of Observed to Expected Cases of Sustained Hypertension Developing Among 22,741 Army Officers According to Certain Preceding Characteristics

Preceding Characteristics		Groups of Army Officers			
		I	II	III	IV
Overweight		−	+	−	+
Transient hypertension		−	−	+	+
Transient tachycardia		−	−	+	+
Person—Years		131,969	33,247	6,720	3,126
Cases later developing sustained hypertension	Observed	244	165	216	137
	Expected	244	67	25	11
Ratio		(1.0)	2.5	8.7	12.3

(From Levy, White, Stroud and Hillman, J. A. M. A. **131**: 951, 1946.)

age groups, subsequent sustained hypertension developed more often in those with previous transient hypertension than in those without. Similarly, the appearance of transient tachycardia, or a temporary elevation of heart rate to 100 or over, was found to be significant.[16] When both transient tachycardia and transient hypertension had been present in a given individual, the incidence of later sustained hypertension was more than twice as great as when either condition was present alone (figure 1).

The same investigators also sought a relationship of overweight to excessive incidence of hypertension in later years.[17] They found that between two and three times as many subjects later developed sustained hypertension who were initially 20 pounds or more overweight as did those who were less heavy. When overweight, transient hypertension and transient tachycardia were *all three* present in the same individual, the rate of

subsequent sustained hypertension was 12 times as high as among those with none of these traits (table 1). They concluded that transient hypertension, or transient tachycardia, or overweight, each by itself increases the probability of the later development of sustained hypertension and of cardiovascular renal disease. The presence of two of these conditions is of greater importance in this respect than any one alone, while the presence of all three is a circumstance of major prognostic significance.

Recently it has been clearly established for the first time that elevation of blood lipids *precedes* clinical coronary disease, rather than being a metabolic result of that disease.[18] The Cooperative Study on Lipoproteins and Atherosclerosis found that "the appearance of clinical manifestations of atherosclerosis is associated with prior elevation, on the average, of the total cholesterol and the S_f 20–100 lipoproteins." Their findings in

TABLE 2

First Appearance of Coronary Heart Disease (New Events) Over a Two Year Period According to Initial Cholesterol Level

	Subjects Divided by Initial Cholesterol	57 Cases of New Events of All Types		37 Cases of Coronary Occlusion	
		No.	Per Cent	No.	Per Cent
Nearly 5,000 normal men, aged 40–59 at the start	Half with higher levels	41	72	32	86
	Median or fiftieth percentile				
	Half with lower levels	16	28	5	14
	Ratio	2.6:1		6.4:1	
	P	0.01		<0.01	

(Adapted from Tables 14 and A-3, Cooperative study on lipoproteins and atherosclerosis, Circulation **14**: 691, 1956.)

regard to cholesterol are summarized in table 2. Cholesterol determinations were carried out at the beginning of the study on nearly 5,000 healthy men 40 to 59 years old, who were mostly industrial workers. In the course of the next two years, 57 of the total group developed some manifestation thought to be definitely related to coronary heart disease, including myocardial infarction, angina pectoris and certain electrocardiographic changes. Seventy-two per cent of those developing such "new events" came from that half of the study population with *higher* initial cholesterol levels—that is, above the median or fiftieth percentile—whereas only 28% came from the half with *lower* initial levels. In other words, more than two and a half times as many "new events" occurred among those with higher levels. Thirty-seven of the 57 "new events" were instances of coronary occlusion (myocardial infarction or coronary thrombosis). This most serious form

of coronary heart disease showed an even greater predilection for the group with *higher* cholesterol levels, 86% of the occlusions occurring in that half of the population.

Nearly 30 years ago, Levine and Brown called attention to the fact that the typical patient with coronary heart disease is a strong, well-set person, muscular and somewhat overweight.[19] They found coronary thrombosis uncommon in thin individuals. In the recent study, "Coronary Heart Disease in Young Adults," Gertler and White demonstrated statistically that the endomorphic mesomorph—the fat, muscular person—is most subject to coronary heart disease, while the ectomorph—the lean person—is least susceptible.[20] Since body type is relatively constant, mesomorphy appears to be an additional trait which frequently characterizes the precoronary individual.

Comparative Incidence of Hypertension and/or Coronary Heart Disease (H+/C+) Among the Offspring of Three Types of Mating.

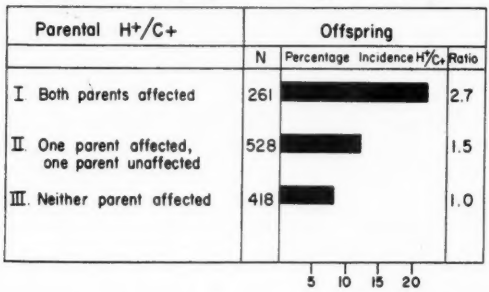

FIG. 2. (Adapted from figure 8, Thomas, C. B., and Cohen, B. H., Ann. Int. Med. **42**: 90, 1955.)

Family history provides another way of classifying healthy individuals. While the exact mode of transmission of hypertension and coronary disease is not yet known, genetic factors are thought to be present. The occurrence of strokes or of heart attacks in successive generations suggests a dominant form of inheritance in regard to both the trait for elevated blood pressure and the apparently independent cholesterol factor. Probably multiple gene action is involved, and the clinical picture presented by the patient largely depends upon the exact constellation of genes in his inheritance.

As part of a long-term study of precursors of hypertension and coronary heart disease in Johns Hopkins medical students, we have previously reported the incidence of these disorders, independently and together, in the grandparents, parents, aunts and uncles.[21, 22] In our analysis of the combined occurrence of hypertension and coronary heart disease in these two successive generations, the proportion of affected offspring was greatest where both parents suffered from some form of these disorders, and least where neither

parent was affected (figure 2). According to whether both, one or neither of the parents was affected, the incidence in the offspring was 22%, 12% and 8%, respectively. Thus, 2.7 times as many offspring of two positive parents were affected by hypertension or coronary disease as were the offspring of two negative parents. The rate for those with one positive parent was intermediate.

In studies on the medical students themselves, we have already described consistent differences in the frequency of "positive" traits among the offspring of affected and nonaffected parents. Figure 3, for example, shows the differences found between the offspring of hypertensive parents and those of normal parents, using a battery of tests related to blood pressure, heart

RELATIONSHIP OF CERTAIN TRAITS TO PARENTAL HYPERTENSION.

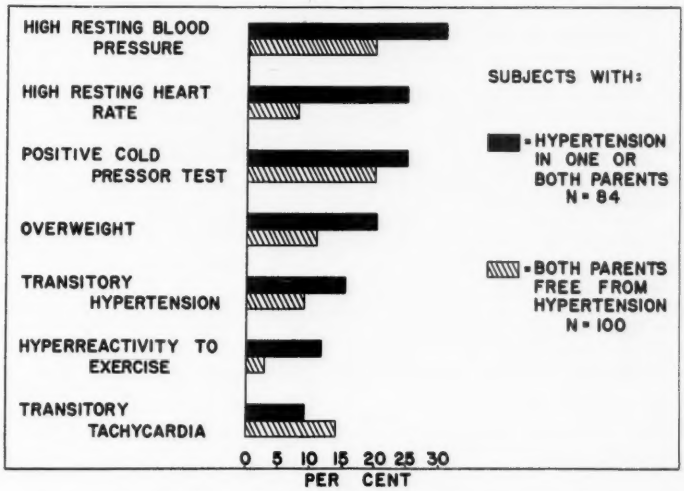
HIGH RESTING BLOOD PRESSURE
HIGH RESTING HEART RATE
POSITIVE COLD PRESSOR TEST
OVERWEIGHT
TRANSITORY HYPERTENSION
HYPERREACTIVITY TO EXERCISE
TRANSITORY TACHYCARDIA
0 5 10 15 20 25 30
PER CENT
SUBJECTS WITH:
HYPERTENSION IN ONE OR BOTH PARENTS N = 84
BOTH PARENTS FREE FROM HYPERTENSION N = 100

FIG. 3. (From Thomas, C. B., Am. J. M. Sc. 224: 367, 1952.)

rate, circulatory hyperreactivity and overweight.[23] In general, the students with positive parental history showed a higher frequency of the traits in question, but the difference between the two groups was often not large.

Figure 4 gives a summary of our findings concerning the prevalence of coronary heart disease among the fathers of subjects with and without hypercholesteremia, that is, cholesterol levels of 300 mg. per 100 c.c. or more on at least one occasion.[24] The difference was clear-cut in every age group of subjects, increasing as the subjects and their fathers grew older. In all, nearly three times as many of the subjects with hypercholesteremia had a parent affected by coronary disease as did subjects with lower cholesterol values.

Time permits only a brief reference to the likelihood that individual psychologic characteristics may someday also serve as measurable guideposts. Studies of personality patterns in patients with hypertension or coronary heart disease have been made by a number of workers.[25–28] Insecurity in childhood, suppressed hostility, obsessive-compulsive tendencies, and subnormal assertiveness are among the factors thought to be significant. Whereas heretofore the subjects had been studied only *after* the onset of disease, most investigators believed that characteristic personality patterns had been present since childhood.

It seems important, therefore, to discover whether such personality patterns are present among young adults before the development of disease. We have approached the difficult problem of measuring significant differences

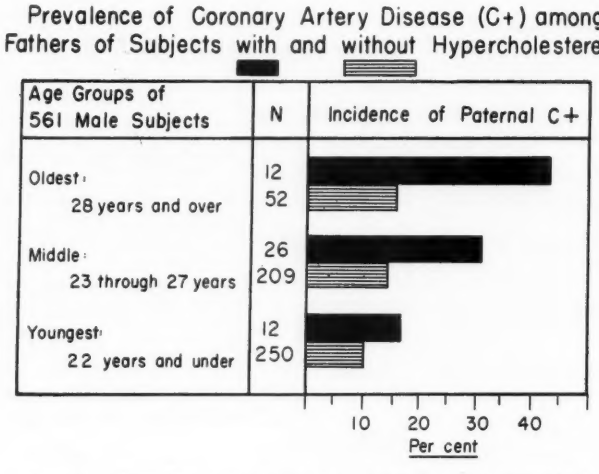

FIG. 4. (From Thomas, C. B., Am. J. M. Sc. 232: 389, 1956.)

in the personality of our subjects from several angles. The Rorschach test has been used as a major tool because of its breadth and objectivity, and because it has been sufficiently standardized to permit statistical analysis. In a preliminary study of the individual Rorschach protocols of 83 medical students, the subjects were divided into groups according to whether parental history of hypertension and/or coronary heart disease was positive, negative or uncertain.[29] When the Rorschach protocols of subjects with positive and negative parental history were compared, they suggested certain differences in temperament (figure 5). Those with a heritage of hypertension or coronary disease showed more aggression-hostility, more obsessive-compulsive trends and more feelings of inadequacy, but less impulsiveness and less total affective reactivity than did their fellows with negative parental history. Therefore, personality traits characterizing hypertensive or coronary patients

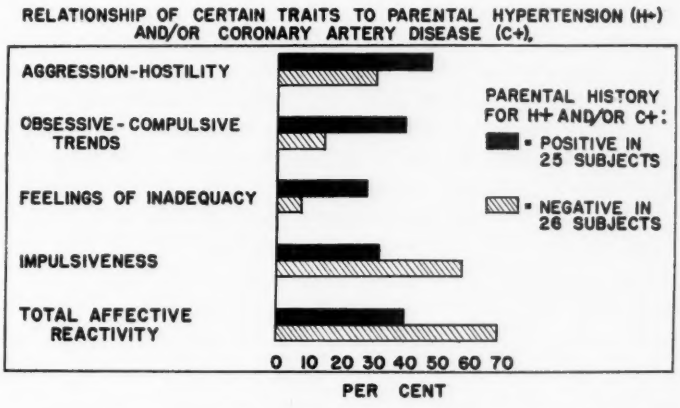
RELATIONSHIP OF CERTAIN TRAITS TO PARENTAL HYPERTENSION (H+) AND/OR CORONARY ARTERY DISEASE (C+),
AGGRESSION-HOSTILITY
OBSESSIVE-COMPULSIVE TRENDS
FEELINGS OF INADEQUACY
IMPULSIVENESS
TOTAL AFFECTIVE REACTIVITY
PARENTAL HISTORY FOR H+ AND/OR C+:
= POSITIVE IN 25 SUBJECTS
= NEGATIVE IN 26 SUBJECTS
0 10 20 30 40 50 60 70
PER CENT

FIG. 5. (From Bruce, J. M., Jr., and Thomas, C. B., Psychiatric Quart. Supplement 27: 207, Part 2, 1953.)

may also be found in a proportion of the offspring before the appearance of disease, but much more work is needed in this phase of the study.

Thus, from all the evidence presented, we see that certain individual traits are found more frequently in those who develop hypertension or coronary disease than in those who do not. However, the presence or absence of any *single* characteristic, such as transient hypertension, does not make enough difference in the attack rate to provide a satisfactory basis for distinguishing susceptible from nonsusceptible individuals.[15-18] Where an individual is characterized by *two or more* significant traits, the difference between the attack rates in the positive and negative groups rises sharply. When, in addition, a person thus characterized has a parent affected with some form of hypertension or coronary heart disease, a new dimension is added to support the view that he may indeed be highly susceptible.

It is therefore proposed that a *four-way* grouping of healthy subjects according to *parental history* and *individual characteristics* be used as the

TABLE 3

Four-Way Grouping of Healthy Subjects as a Basis for Preventive Measures Against Hypertension (H+) and/or Coronary Heart Disease (C+)

Group	Significant Factors		Probability of Developing Disease
	Parental H+/C+	Individual Traits	
I	+	+	High
II	−	+	Fairly high
III	+	−	Doubtful
IV	−	−	Low

basis in selecting highly susceptible individuals for the purpose of testing preventive measures. Such a classification is shown in table 3. Group I, where both the parental and individual factors are positive, stands in sharp contrast to Group IV, where both these significant factors are negative. These two groups are expected to produce the highest and lowest attack rates, respectively. In Group II, where familial and individual factors are discordant, the parent may develop disease later, thus transforming a Group II into a Group I subject, or the traits may be inherited as recessives, or the traits may be due to environmental factors. Group III, also discordant,

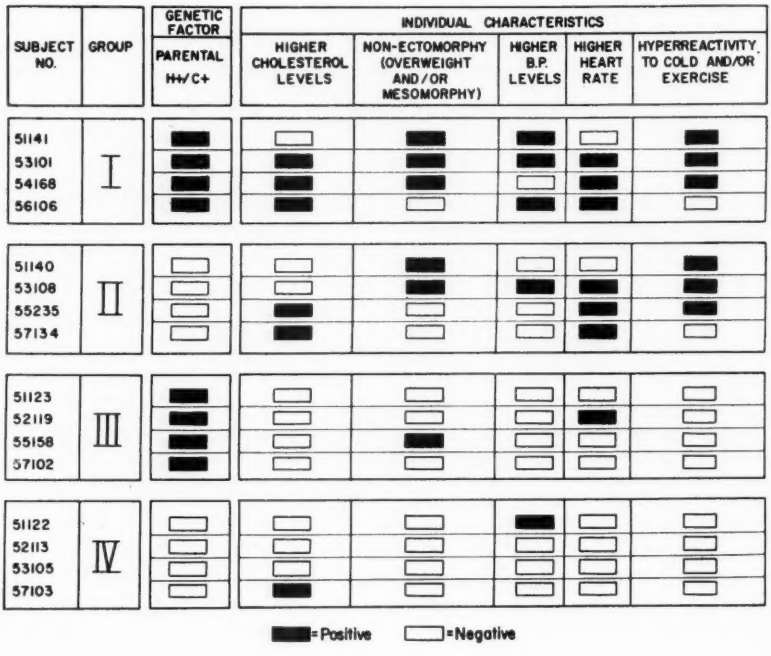

FIG. 6.

includes those who have escaped an adverse inheritance, those who are healthy carriers of recessive traits, and those who may develop positive traits at a later time. Group I provides subjects most suitable for tests of preventive measures.

Examples of subjects from each of the four groups are shown in figure 6. The positive traits appear in varying combinations in different individuals. The likelihood that a single positive characteristic may be fortuitous, or have little meaning in terms of life expectancy, has led us to place persons showing such an isolated trait in the "negative trait" groups. The relative size of

each group depends upon such determinants as the age of parents and the arbitrary limits chosen in defining as "positive" and "negative" traits which actually vary continuously. Using definitions consistent with those previously published, we have found, after reviewing the findings on 534 students in seven consecutive classes, that about one sixth of the subjects fall in Group I, a similar number in Group II, and a few less in Group III. Nearly one third fall in Group IV; the remainder cannot be definitely classified, chiefly because of uncertainty in regard to parental histories.

It must be remembered that these remarks represent our ideas at the present time only. Other important traits, including psychologic determinants, can and undoubtedly will be added. As follow-up studies on these individuals continue to become available year by year, the traits which are the true precursors of hypertension and coronary heart disease will become increasingly clear.

Summario in Interlingua

Vinti annos retro, le prime resultatos de chimoprophylaxe comenciava delinear se. A ille tempore le experimentos concernite con prevenir rheumatic morbo cardiac se monstrava promittente. Le facto que subjectos rheumatic tende a suffrer recurrentias permitteva testar le nove methodo in un gruppo con alte incidentia de attaccos de febre rheumatic. Si nulle tal indices pro le identification de un population susceptibile habeva existite, le effortios a provar le valor de sulfanilamido in le prevention de febre rheumatic haberea essite grandemente retardate. Al tempore presente on recognosce que le uso prophylactic de sulfonamidos e de penicillina resulta in le prevention de plus que 90 pro cento de omne major episodios rheumatic.

Hodie nos dirige nostre speros verso le prevention de morbo cardiac coronari e hypertensive. Successo in le prevention de iste morbos depende del possibilitate de identificar individuos susceptibile ante que irreversibile damnos vascular ha occurrite. Le nunc cognoscite characteristicas que precede hypertension e morbo cardiac coronari e que pote esser usate como guidas in le selection de individuos susceptibile include hyperreactivitate vascular, elevation transitori del pression sanguinee con acceleration del pulso cardiac, excesso de peso, alte nivellos de cholesterol, e le typo particular de conformation corporee que es cognoscite como mesomorphic.

Studios familial conducite in studentes de medicina al Universitate Johns Hopkins indica que le presentia de hypertension e/o morbo de arteria coronari in un o ambe parentes augmenta etiam le probabilitate del occurrentia de ille disordines in le prole. Le presentia o absentia de un sol characteristica specific—per exemplo hypertension transiente—non influentia le incidentia de attaccos sufficientemente pro servir como base satisfactori in le differentiation de individuos susceptibile ab individuos non-susceptibile. Quando un individuo es characterisate per duo o plure tractos significative, le differentia inter le incidentia de attaccos in le gruppo positive e in le gruppo negative se augmenta marcatemente. Si un individuo assi characterisate ha in plus un patre o matre qui suffre del un o altere forma de hypertension o morbo de arteria coronari, un nove argumento supporta le suspicion que ille es de facto multo susceptibile. Per consequente le proposition es formulate que un categorisation quadrivial de subjectos normal secundo le historia parental e le characteristicas personal es usate como base del selection de individuos con alte grados de susceptibilitate pro le objectivos del testation de mesuras preventive. Un categorisation de iste genere es delineate.

Iste remarcas representa nostre ideas in lor stadio currente. Altere tractos de importantia—incluse factores psychologic—va sin dubita esser addite. Il es a expectar que le crescente accumulation de observationes in subjectos studiate a longe vista va resultar in le clarification progressive del tractos que es le ver precursores de hypertension e de morbo cardiac coronari.

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SOME BASIC, UNSOLVED PROBLEMS IN THE PREVENTION OF RHEUMATIC FEVER*

By Alvin F. Coburn, M.D., *Chappaqua, N. Y.*

Physicians concerned with problems in the prevention of rheumatic fever have for more than half a century been confronted with two facts in the epidemiology of this disease. Wherever investigated, it has been observed that (a) outbreaks of rheumatic fever occurred following epidemics of "sore throats" or scarlatina, and (b) onset of the rheumatic state was confined almost exclusively to low income families. The first of these facts has been the subject of widespread research for more than a quarter of a century; the second has not yet received the attention that it deserves. Today I wish to deal briefly with the former and in some detail with the latter. Clarification of the significance of the relation of low income to the pathogenesis of rheumatic fever may reasonably be expected to lead to measures for the eradication of the rheumatic state.

It is well recognized that "sore throats," nasopharyngitis and scarlet fever, which precipitate rheumatic attacks, are infections caused by *Streptococcus pyogenes*. Nevertheless, it is not yet known whether certain strains of group A streptococcus produce "rheumatogenic" substances or form antigenic haptenes. Furthermore, there is no definite indication how streptococci induce rheumatic activity in susceptible subjects. The mechanism whereby *Streptococcus pyogenes* triggers the rheumatic reaction is an unknown that challenges the immunologist and the biochemist. But even more fundamental is the question, What are the factors which together create an epidemic of air-borne hemolytic streptococcal infections? This problem is not new. Physicians have long recognized that scarlatina may be contagious. Moreover, it is known that, following recovery from group A infections, some patients become "dangerous carriers," dangerous in that they give rise to streptococcal diseases among their contacts.

More recently, it has been possible to define some of the problems in the epidemiology of air-borne streptococcal diseases by inducing these infections in laboratory animals exposed to contaminated air. British workers demonstrated that group C streptococcal respiratory tract infections may be induced in ferrets.[1, 2] Subsequently, American workers have shown that fatal group A respiratory tract infections may be caused in mice. The mice were exposed to an aerosol mist contaminated with microörganisms which gave rise to epidemics in man.[3, 4, 5, 6] These observations may be summarized briefly:

* Presented as one of the James D. Bruce Memorial Lectures at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 9, 1957.

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(a) Strains of *Streptococcus pyogenes* associated with the induction of an epidemic of respiratory tract infections in man are pathogenic for the Swiss albino mouse.

(b) The aerosol spray method described for contaminating the atmosphere of an air-tight chamber appears effective in screening streptococci with potential epidemicity for man.

(c) Laboratory observations lend support to the concept that the induction of streptococcal nasopharyngeal infection is not purely a matter of the quantity of microörganisms inhaled. It seems to be determined, in part at least, by qualitative differences in the bacteria contaminating the air.

(d) The induction of fatal streptococcal respiratory tract disease in the mouse appears to be dependent on both an environmental and a bacterial factor.

Some of the basic problems in the epidemiology of *Streptococcus pyogenes* may now be attacked in the laboratory. I shall state only two, and in the barest outline:

1. What is the relation of pathogenicity of group A streptococcus to the metabolism of the microörganism? This relation may be associated with a change in the nutritional status of the bacterial strain and with a resultant change in the metabolism of the bacterial cell. Fundamental information is needed on the differences in the biochemical and physiologic *in situ* activities between the highly pathogenic and the noninfective streptococcal strains. This is now a well defined problem in bacterial metabolism for the microbiologist.

2. What are the environmental factors which determine susceptibility of mice to air-borne pathogenic streptococci? One condition, the external environment, appears to be dependent upon the seasons, that is, on some cosmic factor intimately associated with climate. A second condition is in the internal environment at the site of infection. This appears to be influenced by the presence of inflammation; for example, the inflammation of the respiratory tract as caused by mouse-adapted influenza virus.

Technics must be worked out for obtaining fundamental information on the symbiosis of viral and bacterial agents. On the other hand, methods are available for measuring external environmental conditions. One can reasonably expect that research will provide information on the cosmic conditions which determine whether the experimental animal becomes a healthy carrier or dies of streptococcal disease.

Now may I invite your attention to some challenging problems of the host, the rheumatic subject?

The fact that the highest incidence of rheumatic fever occurs in the lowest income brackets is well documented by many physicians in both hemispheres. I shall refer to only two observers. In America, Paul and his colleagues, writing on *The Social Incidence of Rheumatic Heart Disease,*[7] pointed out: "Our determinations of the incidence of rheumatic heart disease among

poverty stricken and other groups of school children from New Haven and its suburbs seem to bear out the results of our previous studies on University students. They furnish numerical evidence that in and about this particular city of the United States, rheumatic heart disease found its highest prevalence among the poorest children living in an urban environment. The most striking finding was that rheumatic heart disease was eight times as prevalent among pupils attending a school from the poorest section of the city as it was among pupils attending private urban schools from the best residential sec-

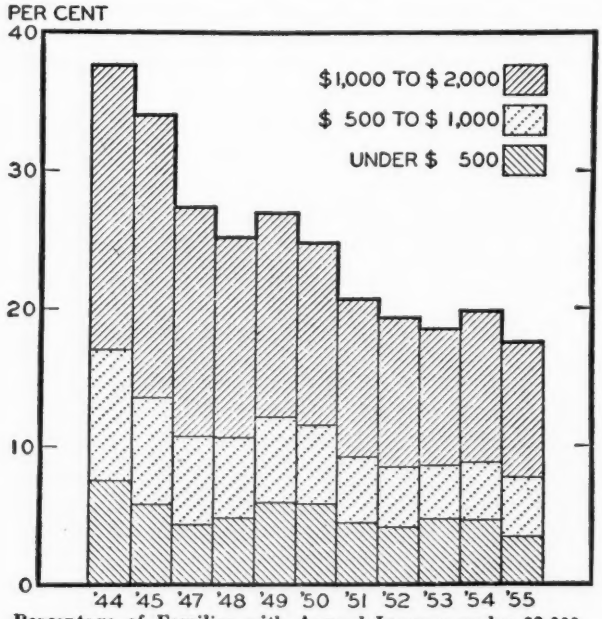
PER CENT
40
30
20
10
0
$1,000 TO $ 2,000
$ 500 TO $ 1,000
UNDER $ 500
'44 '45 '47 '48 '49 '50 '51 '52 '53 '54 '55
Percentage of Families with Annual Incomes under $2,000.
(Bureau of the Census estimates ; no data available for 1946.)

FIG. 1. The decrease in low income families of America.

tions. The average incidence of rheumatic heart disease among pupils attending two urban public schools was about twice that recorded among pupils of a similar age group who attended suburban and rural public schools."

In England, Glover in his Milroy Lectures [8] stated: "No disease has a clearer cut 'social incidence' than acute rheumatism, which falls perhaps thirty times as frequently upon the poorer children of the industrial town, as upon the children of the well-to-do. This subject has been fully discussed in the recent report of the Child Life Committee of the Medical Research Council. I agree, however, with those who hold that the incidence of acute

rheumatism increases directly with poverty, malnutrition, overcrowding, and bad housing."

Glover recognized clearly that rheumatic fever is associated with poverty, and that poverty is accompanied by poor nutrition. The diet of the rheumatic child is usually deficient in many respects.[9] One of these is the ingestion of egg yolk.[10] The limitation on time will not permit my describing the background for the investigation of egg yolk in rheumatic children.[11] But I do wish to present evidence: first, on a possible relation between family income, egg consumption, and the incidence of rheumatic fever; second, an apparent association between the increased consumption of egg yolk and the decrease in rheumatic recurrences.

At the very beginning of this exposition let me emphasize that even in the wealthy America of 1955 there was a large segment of our population living

TABLE 1

Classification of the Population by Income Groups and Average Food Expenditure Per Head in Each Group

Group	Income Per Head Per Week	Estimated Average Expenditure on Food	Estimated Population of Group	
			Numbers	Percentage
I	Up to 10s.	4s.	4,500,000	10
II	10s. to 15s.	6s.	9,000,000	20
III	15s. to 20s.	8s.	9,000,000	20
IV	20s. to 30s.	10s.	9,000,000	20
V	30s. to 45s.	12s.	9,000,000	20
VI	Over 45s.	14s.	4,500,000	10
Average	30s.	9s.	—	—

From *Food, Health and Income*, by Orr, 1936. Reproduced with permission from the British Medical Association.

on less than $2,000 per family per annum. I quote and present a figure from the November, 1956, Monthly Letter of First National City Bank of New York:[12] "The grinding inescapable poverty that existed in much of the nineteenth century has been disappearing in this country. The breadlines and shantytowns of the thirties have vanished. No one need starve or go homeless today whether he has an income or not, so great is the variety of private and government assistance programs. There may be a considerable number of low-income families in this country whose wants outrun their means, but chronic, abject poverty is quantitatively a much smaller problem." Figure 1 shows that about 10% of American families had an income of less than $1,000.

In England, prior to World War II, 10% of the people had an income of less than 10 shillings per week. Orr[13] showed that "the consumption of protective foods varied directly with changes in income." In the British population of 1936 there were 10% who spent only about 4 shillings per head per week. This is shown in table 1.

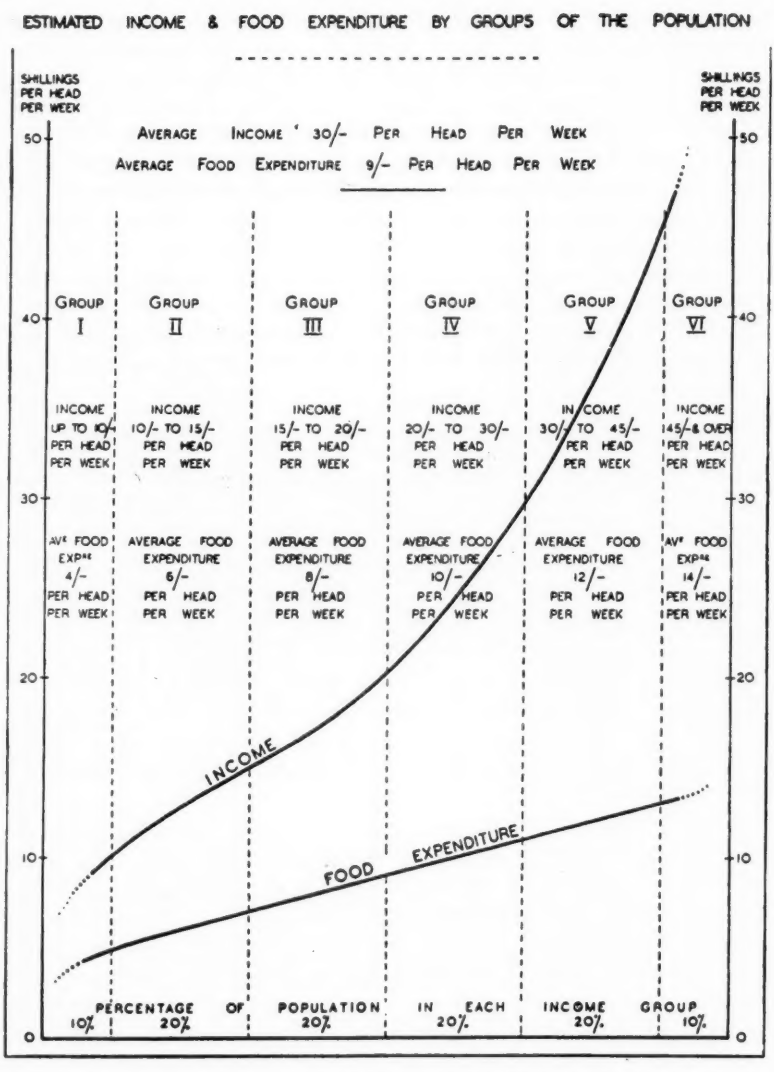
ESTIMATED INCOME & FOOD EXPENDITURE BY GROUPS OF THE POPULATION
SHILLINGS PER HEAD PER WEEK
AVERAGE INCOME 30/- PER HEAD PER WEEK
AVERAGE FOOD EXPENDITURE 9/- PER HEAD PER WEEK
GROUP I
INCOME UP TO 10/- PER HEAD PER WEEK
AVE FOOD EXPE 4/- PER HEAD PER WEEK
GROUP II
INCOME 10/- TO 15/- PER HEAD PER WEEK
AVERAGE FOOD EXPENDITURE 6/- PER HEAD PER WEEK
GROUP III
INCOME 15/- TO 20/- PER HEAD PER WEEK
AVERAGE FOOD EXPENDITURE 8/- PER HEAD PER WEEK
GROUP IV
INCOME 20/- TO 30/- PER HEAD PER WEEK
AVERAGE FOOD EXPENDITURE 10/- PER HEAD PER WEEK
GROUP V
INCOME 30/- TO 45/- PER HEAD PER WEEK
AVERAGE FOOD EXPENDITURE 12/- PER HEAD PER WEEK
GROUP VI
INCOME 45/- & OVER PER HEAD PER WEEK
AVE FOOD EXPE 14/- PER HEAD PER WEEK
INCOME
FOOD EXPENDITURE
PERCENTAGE OF POPULATION IN EACH INCOME GROUP
10% 20% 20% 20% 20% 10%
0 10 20 30 40 50

FIG. 2. From *Food, Health and Income,* by Orr, 1936. Reproduced with permission from the British Medical Association.

Orr showed that as income increased the total food expenditure increased. This is shown in figure 2.

But, according to Orr, the expenditure for certain foods remained level; whereas in the cases of other foods (for example, eggs), the increase was progressive. This is shown in figure 3.

TABLE 2

Quantities of Food Consumed Per Head Per Week at Different Income Levels in 1,152 Family Budgets

	Group I	Group II	Group III	Group IV	Group V*	Group VI*	Weighted Average of Groups
Proportion of the population	10%	20%	20%	20%	20%	10%	
Number of budgets	411	152	233	156	136	64	—
Beef and veal, ozs.	9.5	11.5	11.7	11.3	10.2	9.5	10.8
Mutton and lamb, ozs.	2.1	3.1	4.3	6.2	6.8	9.7	5.3
Bacon and ham, ozs.	2.6	4.1	4.6	5.7	5.7	6.6	4.9
Other meat, ozs.	2.8	2.9	4.2	5.4	3.6	3.5	3.8
Total meat, ozs.	17.0	21.6	24.8	28.6	26.3	29.3	24.8
Bread and flour (excl. biscuits and cakes), ozs.	64.5	62.0	63.3	64.7	54.6	47.7	60.1
Milk—fresh, pints	1.1	2.1	2.6	2.9	4.5	5.4	3.1
Milk—condensed, pints	0.6	0.4	0.4	0.3	0.2	0.1	0.3
Eggs, number	1.9	2.8	3.7	4.8	4.7	5.2	3.9

From *Food, Health and Income*, by Orr, 1936. Reproduced with permission of the British Medical Association.

Orr's actual data indicate that families living on less than 10 shillings per head per week may consume 1.9 eggs per head per week. In contrast, families living on at least 45 shillings per head per week had 5.2 eggs per head per week. These data on egg consumption are shown in table 2. Orr states: "From a survey of egg consumption it is concluded that egg consumption is primarily a matter of income." [13]

The British diet of 1936 was markedly altered by war rationing.[14] A relatively simple diet, but an adequate one, was enforced on all persons. The Report of *The Committee on Nutrition* has pointed out that "consumption level studies demonstrate some remarkable features of wartime and postwartime food supplies." [14] This was especially striking for milk and eggs.

Table 3 shows the increase in total egg consumption during the war and postwar years.

The striking increase in total egg consumption during the war years was a result of the importation of egg yolk. This gave rise to numerous epidemics of salmonella infections caused by powdered egg yolk.[15] Neverthe-

TABLE 3

Ministry of Food National Food Survey
Food Consumption in the Home—Urban Working-Class Households

Food	1942	1943	1944	1945	1946	1947
Eggs—Total (equiv. number)	1.40	2.22	2.93	3.01	2.50	2.30
Shell (number)	0.92	0.83	0.94	1.27	1.41	1.60

From the British Medical Association Report of the Committee on Nutrition, 1950. Reproduced with permission from the British Medical Association.

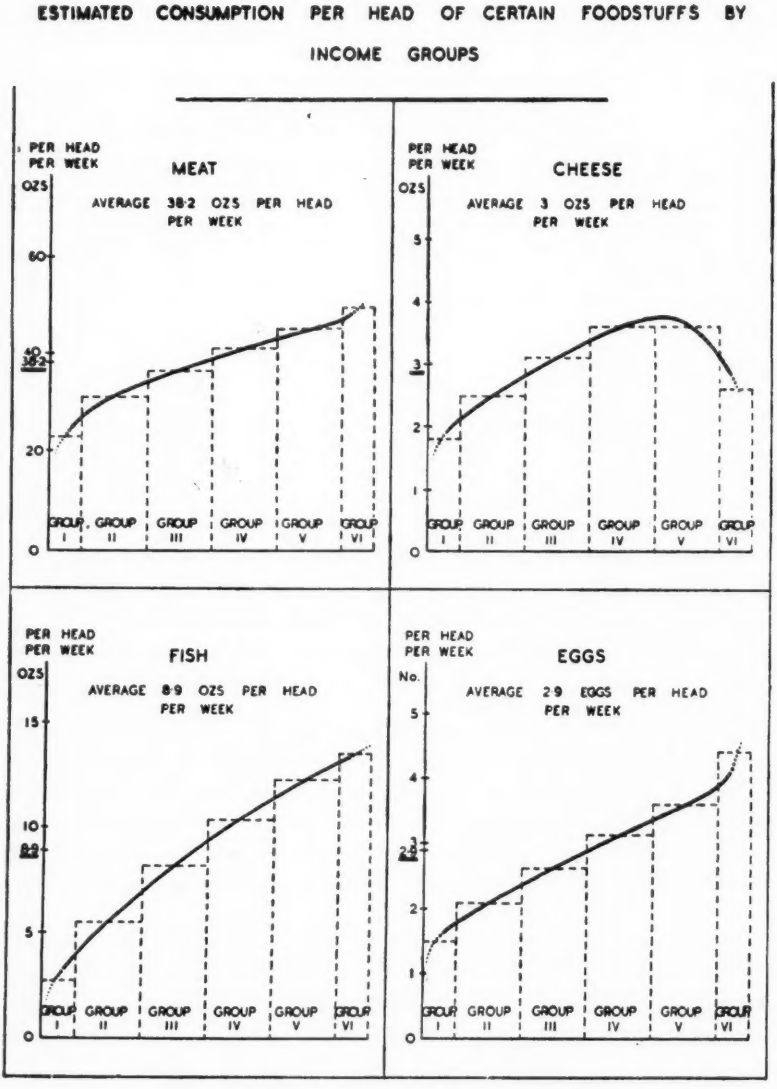

FIG. 3A. From *Food, Health and Income*, by Orr, 1936. Reproduced with permission from the British Medical Association.

less, powdered egg yolk was considered such an important factor in the British diet that it was rationed officially to all persons throughout the war. In fact, between 1942 and 1945 the British diet was supplemented by 244,000 *tons* of egg yolk.[16] Perhaps the aspect of wartime rationing most significant

to the rheumatic problem was the fact that *urban children of the lowest income brackets* received milk and eggs. This was the group that had not received egg yolk prior to the war and that had developed most of the rheumatic fever observed in the United Kingdom.

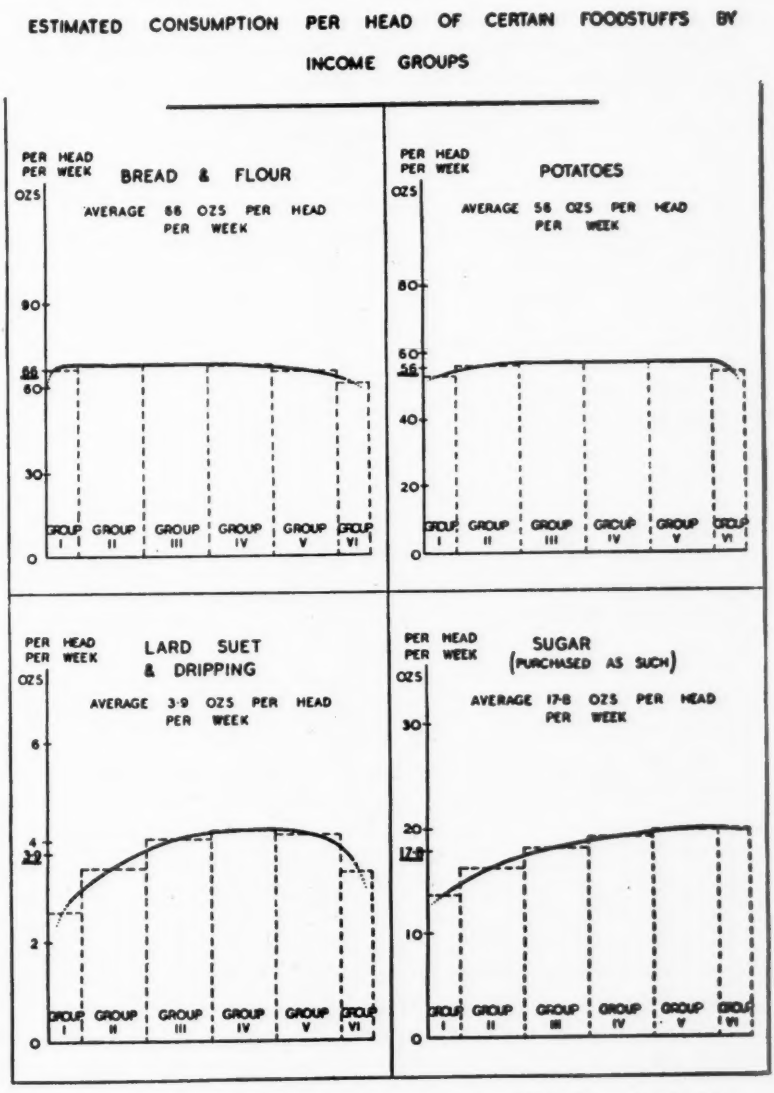

FIG. 3B. From *Food, Health and Income*, by Orr, 1936. Reproduced with permission from the British Medical Association.

Your attention is called to this matter because, although an "uncontrolled experiment," this wartime rationing represents an enforced change in diet for more than 40,000,000 persons over a period of years. Furthermore, this marked change in diet habits has persisted ever since World War II ended.

And now I ask you to examine with me the clinical changes that have occurred in the rheumatic picture. Since World War II British physicians have repeatedly called attention to the changing picture of "juvenile rheumatism" in the United Kingdom.[17, 18–19] This became striking in the period of 1940–55 prior to the availability of penicillin or the use of chemoprophylaxis.

TABLE 4

Admissions to Great Ormond Street for Juvenile Rheumatism in Selected Years, 1869–1950

Years	Physicians	Total Medical Admissions	Rheumatism and Chorea. Total and as % Medical Admissions	Deaths from Rheumatism. Total and % all Cases Rheumatism
1869 1870	West Dickinson	472	74 (15.7%)	6 (8.1%)
1889 and 1891	Cheadle Sturges Barlow Lees	1,117	176 (15.7%)	13 (7.4%)
1919 1920	Voelcker Colman Still Poynton Hutchison Thursfield	2,519	262 (10.8%)	22 (8.4%)
1949 1950		4,917	31 (0.6%)	0

From Cox and Schlesinger, 1956. Reproduced with permission of Dr. Bernard Schlesinger.

In Chicago we too observed a similarly changing picture among some groups during 1946–56. For example, we noted a striking change in the Bridgeport District of some 50,000 persons. This District had more than 300 rheumatic children; the expectancy had been at least one new rheumatic child per thousand per year; a recurrence rate of at least 20% among rheumatic children below the age of 16 was also expected. However, in spite of the usual incidence of streptococcal infections, new cases and recurrences of rheumatic fever became a rarity. This Bridgeport District of Chicago had a Caucasian population in which both the family income and the amount of dollars spent on food rose markedly during the postwar years. Egg consumption was approximately seven per person per week. In sharp contrast, another district of Chicago, with a Negro population, experienced poverty with little rise in income and no significant improvement in diet. This group

fell into the lowest economic 10%. Egg consumption was approximately two and one-half per person per week. The incidence of rheumatic fever, both first attacks and recurrences, remained at a high level.

Our observations have been limited to a small group. However, the changing picture of the incidence of rheumatic fever observed in Britain was made on a large population and is well documented. Four illustrations will establish the point. First, at the great Ormond Street Hospital, Cox and

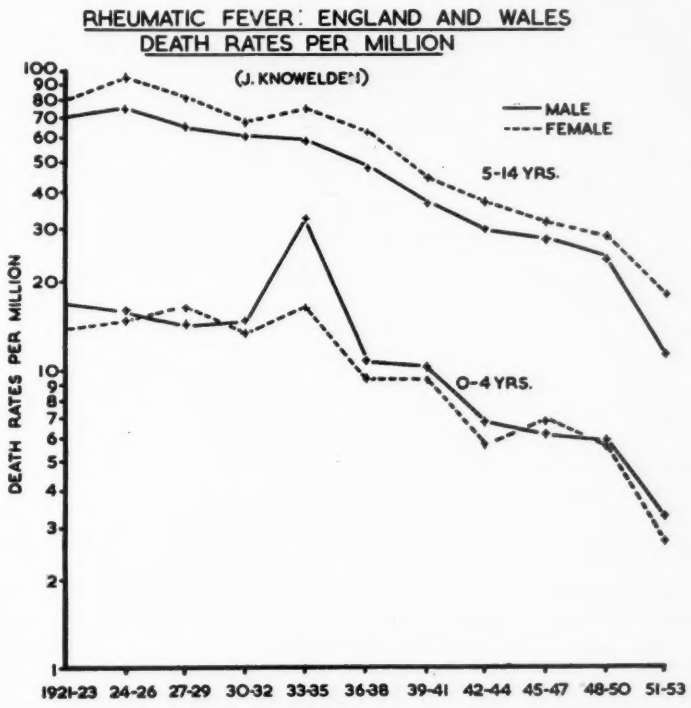

FIG. 4. From Conybeare, 1951. Reproduced with permission of Dr. J. Knowelden from report by Cox and Schlesinger.

Schlesinger [17] showed that the admission rate for rheumatic fever fell strikingly from the range of 10 to 15% to 0.6% in 1949–50. In another table, Cox and Schlesinger showed that no deaths occurred for the four year period, 1946–50. The decrease in hospital admissions for rheumatic fever is shown in table 4.

Second, the declining death rate for rheumatic fever was not limited to the Great Ormond Street Hospital. Throughout England and Wales the rheumatic death rate for children fell markedly between 1938 and 1953. This is shown in figure 4.

Third, Conybeare [18] has pointed out that in 1928–1938 The London County Council, in determining the number of beds required for children with rheumatic fever, concluded that the expectancy was two new cases per 1,000 per annum. Between 1939 and 1949 this expectancy fell to one third or one quarter.

Finally, in eight districts of England, where rheumatic fever of childhood is reportable, it has been observed that the incidence of rheumatic fever for the period 1948–55 has fallen progressively from 0.55 to 0.12 for the annual rate per 1,000 children.[19] This is shown in table 5.

At this point it must be emphasized that it is not known whether there is any direct association between the improved nutrition of the urban children of England's lowest economic group and the improved rheumatic fever statistics for attack rate, hospital admission rate, convalescent care requirements and death rate. However, I do wish to point out that a nutritional

TABLE 5

Notifications of Acute Rheumatism under 16 Years of Age: Certain English Areas 1948–55

Year	Total Children at Risk	Notifications Accepted as Acute Rheumatism	Annual Rate Per 1,000 Children
1948	309,000	170	0.55
1949	313,440	110	0.35
1950	318,900	141	0.44
1951	509,069	130	0.26
1952	510,190	133	0.26
1953	510,030	149	0.29
1954	511,300	146	0.28
1955	511,100	63	0.12

From Hewitt and Stewart, 1952. Reproduced with permission of Dr. E. T. Conybeare.

study was made in Chicago to determine whether there may be an association between the recurrence of rheumatic fever and the consumption of egg yolk. Prior to this Chicago study in the prevention of rheumatic recurrences, our diet surveys showed that egg consumption was lowest in the Negro population referred to above, the group in which income was extremely low and the incidence of rheumatic recurrences high. Without otherwise changing the family diet of these underprivileged children we supplied a supplement of an egg yolk fraction, the alcohol-soluble material, twice daily. The results of early investigations and recent tests, made throughout the winter and spring months of 1952–56 on approximately the same children, can be summarized briefly.

(a) *Nutritional surveys* were made prior to World War II in New York and subsequent to World War II in Chicago. In New York City, diets of private school girls, where not a single case of rheumatic fever had occurred in 10 years, were compared with the diets of rheumatic fever children living in the same neighborhood. The private, Brearley School girls had adequate

diets, including eggs, whereas rheumatic children of the same ages who lived only a few blocks away had multiple dietary deficiencies.[9] In Chicago an associate, Trulson (Ph.D. thesis, Harvard University School of Public Health), analyzed the diets of boys and girls attending a private school, a public school for Caucasian children, a public school for Negro children, and a rheumatic fever children's clinic containing a mixed group. There were striking multiple deficiencies in diet among the children of the rheumatic clinic and in the Negro public school. One deficiency was egg consumption. The differences in the weekly consumption of eggs between the private school and public school groups was statistically significant in all age and sex groups except boys over 12. The private school and Caucasian public school were found to have a relatively low incidence of rheumatic fever. In these four groups a deficiency in egg consumption paralleled the incidence of rheumatic fever. Furthermore, familial studies in the private school group, where egg consumption met standard requirements, showed that the exceptionally low incidence in this group could not be attributed entirely to genetic factors, e.g., there was a high incidence of rheumatic fever among the parents, uncles and aunts of the private school children. In brief, although the two nutritional studies were made a decade apart in New York and Chicago by different technics, they both indicated that children who escaped rheumatic fever generally had adequate diets, whereas in groups of rheumatic children, or in schools with a high incidence of rheumatic fever, there were multiple dietary deficiencies. One of the foods usually subnormal in the diet of the rheumatic child was the egg.[20]

(b) *Supplementation of diets* of rheumatic fever children was done both in New York City with eggs or with whole powdered egg yolk, and in Chicago with fractions of powdered egg yolk.

No attempt will be made to review the various investigations on many factors in the environment of the rheumatic child made over a period of years by our group. Overcrowding usually existed, but in general the results were similar to the findings of others, i.e., not enlightening. By elimination, the author was left with the factor of a poor diet. Furthermore, observations made by our group in a number of cities where rheumatic fever is prevalent showed that the egg is one food that is generally more readily available to rural than to urban children, and it is consistently more frequently used in the diets of families with wealth than those in poverty. As pointed out, Orr has summed up the matter by stating that, in urban populations, "egg consumption is primarily a matter of income." [13] But rheumatic fever was observed occasionally among families with excellent diets, in children who apparently lacked nothing: housing was magnificent, there was no overcrowding, money was abundant, there was no malnutrition and, in fact, the children appeared exceptionally well nourished. Over a period of two decades the author was able to collect a group of 20 such rheumatic children among highly privileged families, and it was found that all but one of these

subjects—because of an allergy, cyclic vomiting, a distaste for egg yolk, or medical advice (albumin in the urine)—had avoided eggs in childhood.

Because of these and other suggestive observations, and because the addition of eggs to the diets seemed harmless, preliminary feeding studies were made. Our observations made on rheumatic children receiving egg yolk supplements are listed herewith chronologically:

1. A two-year study of reinforcement of diet with four egg yolks daily at a convalescent rheumatic home where the subjects were under continuous observation. No other change in diet was made and no significant medications were given. The group included quiescent rheumatic children (44 patient years) who contracted 24 proved group A streptococcal infections with many serologic types (6, 9, 11, 13, 18, 24, 27, 28 and 29). All 44 patients having 24 "challenges" escaped clinical evidences of rheumatic recurrences. This was in sharp contrast to the previous 10 years' experience, in which rheumatic recurrences occurred annually either sporadically or in epidemic outbreak.

2. Two-year study of reinforcement of diet of rheumatic children living at home.[11] It was not possible to get full bacteriologic information on these subjects, but it was possible to omit all medications and reinforce the diet during winter and spring months. There were between 25 and 35 children in each of three groups studied:

A. Rheumatic untreated controls on their normal diet had a recurrence in 11 of 29 instances.

B. Rheumatic subjects on a diet reinforced daily with two eggs, one quart of milk, meat, butter, haliver oil, viosterol, etc., had recurrences in three of 35 instances.

C. Rheumatic subjects on a diet reinforced only with powdered egg yolk (equivalent to six eggs daily) had a recurrence rate of one of 25 instances.

It was planned to select these rheumatic children at random; however, children who were unwilling to take the diet as planned ended up in the control group. Nevertheless, on the basis of their past histories, all subjects were believed to be highly susceptible.

3. Two-year study of reinforcement of diets of rheumatic children for a period of three weeks from onset of hemolytic streptococcal pharyngitis. All of these were proved group A infections. Each patient was administered egg yolk powder, taking the equivalent of four egg yolks daily. The egg yolk was discontinued after three to four weeks of administration. No medication was given during this three-week period. Among rheumatic subjects who received the egg yolk, one of 28 developed rheumatic activity, whereas among the "controls" on their normal diets, 10 of 28 developed rheumatic activity. The "control" group consisted of patients who did not report their acute infections during the febrile period.

4. A one year study in which about 40 children received a supplement of egg yolk protein. This study was discontinued because of rheumatic recurrences.

5. Finally, a four-year study in which the normal diet was reinforced with the alcohol-soluble material (ASM) of egg yolk, conducted in Chicago, 1952–1956. No other changes in diet were made and no sulfonamide or antibiotic was administered. On the average, 35 highly susceptible rheumatic subjects were given the supplement. The equivalent of six egg yolks was advised; approximately half of this was actually consumed. All but one of the children were under 15 years of age.

Over the four-year period a total of 45 children who were considered to be highly susceptible rheumatic subjects were under investigation. Thirty-five of these subjects were "challenged" with at least 68 streptococcal infections of many serologic types. All but five of these group A infections failed to induce clinical or laboratory evidences of rheumatic activity in these highly susceptible rheumatic children over a period of four years. Because of penicillin availability and current policies, it was not possible to have an appropriate untreated "control group." However, on the basis of previous experience, recurrences were to be expected after at least 17 of these streptococcal infections.

In conclusion, may I point out that we physicians of 1957 lack the fundamental knowledge essential for preventing the rheumatic state. We do not understand the conditions, i.e., the properties of bacteria and the factors of environment which make possible air-borne streptococcal respiratory tract epidemics. Furthermore, we have not yet acquired basic information on the biochemical mechanisms within the host which determine rheumatic susceptibility. I leave for your consideration the concept that one factor in rheumatic susceptibility may well be the nutrition of childhood, and the hope that perhaps an essential part of this factor will eventually be isolated from the yolk of an egg. If this concept be false, there remains unsolved the all-important problem, What is the significant factor in the "social incidence" of rheumatic fever? If, however, this concept be true, one may reasonably expect that administration of adequate amounts of the significant dietary supplement throughout pregnancy, infancy and childhood will lead to the eradication of the rheumatic state.

ACKNOWLEDGMENT

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SUMMARIO IN INTERLINGUA

Il pare que febre rheumatic es un morbo "de summation." Le maturation del stato rheumatic depende essentialmente del coincidentia del effectos de plure factores. Duo de istos, que pote esser investigate, es le factor del infection e le factor del responsa del subjecto. Le nonresolvite problemas connectite con iste duo punctos es innumerabile.

Le factor del infection subleva le interessante question: Como pote streptococco hemolytic gruppo A inducer aero-transmission de morbo del vias supero-respiratori

in humanos? Apparentemente iste capacitate depende de (a) un certe qualitate del bacterio, probabilemente metabolic, e (b) certe conditiones extrinsec in le atmosphera, probabilemente physic. Ultimemente il es possibile que tanto (a) como etiam (b) va esser recognoscite como aspectos del conditiones in le ambiente local del sito del infection.

Altere questiones: Proque es solmente un basse procentage del humanos susceptibile a febre rheumatic, e proque es le maturation del morbo restringite quasi completemente a circulos de basse ressources financiari? Recente observationes suggere que le factor del "basse ressources financiari" es possibilemente un factor nutritional. Iste aspecto del "chimismo del organismo hospite" es discutite.

Si febre rheumatic es un morbo "de summation," su maturation pote esser prevenite per le interruption del action de non importa le qual del factores que es essential pro le pathogenese del stato rheumatic. Methodos pro le prevention de recurrentias rheumatic es jam in existentia. Methodos pro le eradication de susceptibilitate rheumatic es sub disveloppamento. Un urgentissime desiderato es informationes fundamental in re tanto le infectivitate de *Streptococcus pyogenes* como etiam le chimismo in le organismo del subjecto rheumatic.

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CARBARSONE TOXICITY: A REVIEW OF THE LITERATURE AND REPORT OF 45 CASES *

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INORGANIC arsenic has been employed empirically in therapeutics for centuries. Modern use of the drug dates from the researches of Paul Ehrlich into syphilotherapy, during which time he synthesized and tested the treponemicidal effect of organic arsenicals, including stovarsol and carbarsone. Marchoux [1] demonstrated stovarsol to be amebicidal. Carbarsone (4-carbaminophenyl-arsonic acid) was shown to be amebicidal by Reed,[2] since which time it has been employed extensively in antiamebic therapy. Reports of toxicity to this compound have been remarkably few, in sharp contrast to inorganic arsenic and the organic compounds formerly widely employed in syphilotherapy.

In reviewing the literature of carbarsone toxicity we found many reports couched in generalities. Specific cases have been reported by Smithies,[3] von Hagen et al.,[5] Anderson and Reed,[6] Epstein [7] and Nelson.[8] Those reported by Smithies [3] consisted of exfoliative dermatitis (one case), laryngeal and pulmonary edema (one case), ankle edema, joint aches and hepatomegaly (this case was treated with dosage now known to be excessive), facial and retinal edema, cylindruria and albuminuria (overdosage occurred in this case), diarrhea, nausea, vomiting and abdominal pain (this case is thought by us to represent a Herxheimer reaction [4]), and icterus (one case in which no further details are afforded). Von Hagen et al.[5] observed two cases of encephalopathy due to carbarsone, both of which resulted from overdosage; and Anderson and Reed [6] reported icterus, right upper quadrant abdominal pain and hepatomegaly in one case. (Overdosage may have been a factor, since it is stated that the patient had been repeatedly treated with carbarsone.) Epstein's [7] case of exfoliative dermatitis is the only reported fatality from carbarsone that we were able to find in the literature.

Epstein's case also had fatty infiltration of the liver, but this is considered by us to be a manifestation of nutritional liver disorder, since the patient had been critically ill and vomiting for a considerable period before death. Nelson [8] has recently reported two additional cases of liver damage thought to be due to carbarsone. His first case developed mild hepatocellular disorder following a course of carbarsone for amebiasis. Liver biopsy was normal. We are reluctant to accept this as carbarsone toxicity on the

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evidence presented, in spite of dosage in excess of that which we believe safe. Nelson's second case developed obstructive jaundice during carbarsone therapy, coupled with symptoms consistent with carbarsone toxicity.

Review of the material on file in the Armed Forces Institute of Pathology revealed but one case coded "carbarsone toxicity." This was a case of hemorrhagic encephalopathy with normal cerebrospinal fluid protein (34.5 mg./100 ml.) Arsenic content of brain was 0.035 mg./100 gm.

This present report concerns 45 cases of toxic reactions to carbarsone which have occurred during carbarsone therapy of more than 1,500 cases of amebiasis in our military practice (table 1). In the majority of these cases the initial findings were fever, epigastric burning, abdominal pain, diarrhea, nausea and vomiting. The epigastric pain was severe and long-lasting, with associated intestinal hypermotility and epigastric and liver tenderness. In 36 of the cases there was no further progression of the reaction on discontinuance of the medication. British anti-lewisite (BAL), 10% in oil, was given intramuscularly to the severest cases, with a dramatic response often beginning as promptly as two hours after the first dose.

TABLE 1

Type of Toxicity in 45 Cases of Carbarsone Poisoning

Organ or System Involved	No. Cases
Gastrointestinal alone	36
Nervous system alone	1
Nervous system and gastrointestinal	4
Dermatologic alone	1
Dermatologic and gastrointestinal	2
Nervous system, hepatic and gastrointestinal	1
Total number cases	45

Progression to exfoliative dermatitis occurred in three cases, central nervous system involvement developed in five cases, and in one case there were both central nervous system and hepatic involvement.

In the arsenic encephalopathy group, severe headache usually occurred first, followed rapidly by apprehension, disorientation, delirium, delusions and convulsions. Two of this group died in spite of anticonvulsant and BAL therapy. In both of these cases the carbarsone employed was subsequently shown to be contaminated with arsanilic acid (vide infra). In addition, gross overdosage occurred in a child whose disease was further complicated by the presence of a pathogenic strain of *Escherichia coli*. The other fatal case had received a severe head injury in battle a few weeks before, and it is believed that this lowered his tolerance to the arsenical. Analysis of tissue for arsenic content revealed levels, expressed as arsenic, of 3.0 mcg./gm. of liver and 0.5 mcg./gm. of brain in the first case and 3.0 mcg./gm. of liver and 0.4 mcg./gm. of brain in the second case. The microscopic appearance of the brain was essentially typical of early arsenic encephalopathy as described in textbooks of pathology.

It is to be noted that lumbar puncture in three of these patients revealed elevated spinal fluid protein levels without other chemical or cellular abnormalities. Spinal fluid was not examined in the remaining cases, one of which was a fatality.

One case developed a toxic psychosis which appeared to be an exacerbation of an underlying psychosis. It seems that her usual psychotic reaction pattern was transiently accentuated during the toxic episode. Her spinal fluid proteins at this time were 160 mg.%.

An instance illustrating toxicity involving the nervous system is presented.

Case Reports

Case 1. A 29 year old white female was first seen as an outpatient for complaint of intermittent diarrhea. Sigmoidoscopic examination revealed lesions characteristic of amebiasis, and specimens aspirated were positive for *E. histolytica.* Therapy consisted of carbarsone, 0.25 gm. twice daily, and quinacrine, 0.1 gm. three times daily. Over a five day period the patient developed epigastric distress, nausea, vomiting, diarrhea, apprehension and abdominal cramps, for which she was hospitalized for BAL therapy.

Physical examination was normal except for generalized abdominal and hepatic tenderness. Before BAL could be administered the patient complained of scotomata and vomited, then minutes later developed status epilepticus. Sodium amytal and paraldehyde were used to control the convulsive seizures, and BAL was immediately started and a full course of therapy given. Subsequent to the first dose of BAL the patient convulsed once. She gradually improved through semicomatose periods, disorientation and headaches to normal over a five day period. Multiple spinal fluid examinations revealed pressures of from 122 mm. H_2O to 282 mm. H_2O, and proteins of 140 to 320 mg. % as the only abnormalities. There was no evidence of renal or hematopoietic toxicity. The patient's recovery was complete except for anosmia. Diodoquin and quinacrine were subsequently successfully employed to treat the amebic infection.

Dermatologic reactions were noted in three patients. These were considered typical examples of exfoliative dermatitis. Two of the three also had severe gastrointestinal reactions. All were treated with BAL, with rapid and complete recovery, evidence of desquamation persisting a week or more after therapy.

Case 2. A 46 year old white male was hospitalized with the complaint of severe intermittent diarrhea, lower abdominal cramps and occasional right upper quadrant pain. He had been treated 17 years previously with neoarsphenamine and bismuth for syphilis.

Physical examination revealed fever (99.4° F.), a tender liver palpable 2 to 3 cm. below the right costal margin, and tenderness of the sigmoid colon. No other abnormalities were evident.

Laboratory data, including complete blood count, serology, urinalysis and chest x-ray, were normal. Sigmoidoscopy revealed many isolated ulcerations and miliary abscesses. Aspirated specimens from these lesions were positive for *E. histolytica.*

Therapy consisted of carbarsone, 250 mg. three times daily, and quinacrine, 100 mg. four times daily. The patient experienced epigastric burning soon after ingesting the initial dose of carbarsone. The discomfort persisted and was associated with

nausea without vomiting. After the second dose he complained of diarrhea, generalized pruritus, increased discomfort and malaise, so carbarsone was discontinued. Several hours later a fine maculopapular rash appeared which involved the palms, soles, flexor surfaces and body folds. The next day his temperature was 101° F.; epigastric burning and pruritus persisted, and a branny desquamation was evident involving the palms and flexor surface of the forearms. Leukocytosis of 12,500 was present, with 7% eosinophilia. Arsenical exfoliative dermatitis was diagnosed and BAL treatment was instituted. Within two hours of the first dose the patient was subjectively improved, fever was reduced, epigastric burning was absent and the skin was less erythematous. BAL was continued, but the desquamation was still visible a week later. Since amebiasis persisted the patient was treated with quinacrine and diodoquin, with complete, uneventful recovery.

One case who developed toxic psychosis and intrahepatic biliary obstruction is reported in detail.

Case 3. A 41 year old white male was first seen as an outpatient for complaints of reduced exercise tolerance, malaise and intermittent diarrhea.

Physical examination revealed "liver palms" and a tender, enlarged liver; all other findings were normal. Laboratory data were normal except for a borderline alkaline phosphatase (11.9 SJR units). Sigmoidoscopy revealed superficial erosions compatible with the lesions produced by *E. histolytica,* and a clinical diagnosis of amebiasis was made. Carbarsone, 0.25 gm. three times daily, and quinacrine, 0.1 gm. four times daily, were prescribed. Six days later the patient complained of nausea, vomiting, diarrhea, anorexia and nervousness; Herxheimer's reaction was thought to be present and therapy was discontinued for a day, then resumed. Gastrointestinal symptoms recurred with increased severity and apprehension became obvious.

TABLE 2

Summary of Laboratory Data on Case 3

Total bilirubin	0.7	19.2	19	18.5	28	26.5	20.5	10
Alkaline phosphatase	11.6	19.6	17	12.6	16	21.1	16.1	16.8
Total cholesterol	207	770	810	510	228	176	284	337
Cholesterol esters (%)	71	21	20	29	29	14	18	20.2
Cephalin-cholesterol flocculation		Neg.	Neg.	Neg.	Neg.		Neg.	
Thymol turbidity	3	5	5	3	1			
Urine urobilinogen		.4	.26	0		0	137	8.9
Prothrombin time		100	100		100	100		
Time in weeks	0	2	4	6	8	10	12	14

The patient was hospitalized and treated symptomatically, with good response. Carbarsone was taken sporadically for the next four days, when headache, disorientation and delusions became manifest. Medications were discontinued and in four days all mental aberrations cleared. Spinal fluid protein was 106 mg. %. The patient was noted to be jaundiced, and liver functions revealed a total bilirubin of 21.6 mg. % and an alkaline phosphatase of 19. The cephalin-cholesterol flocculation, Kunkel and thymol turbidity tests were normal and remained so (table 2). The biliary obstruction continued unabated for six weeks, at which time laparotomy was performed. No evidence of extrahepatic obstruction was discovered. Liver biopsy taken at that time revealed normal tissue except for bile plugs in small canaliculi. The tissue contained no demonstrable arsenic (figure 1).

FIG. 1 *A*. Liver biopsy from case 3. Normal architecture of liver cords. *A* represents bile plugs in canaliculi; *B*, areas of intracellular bile deposits.

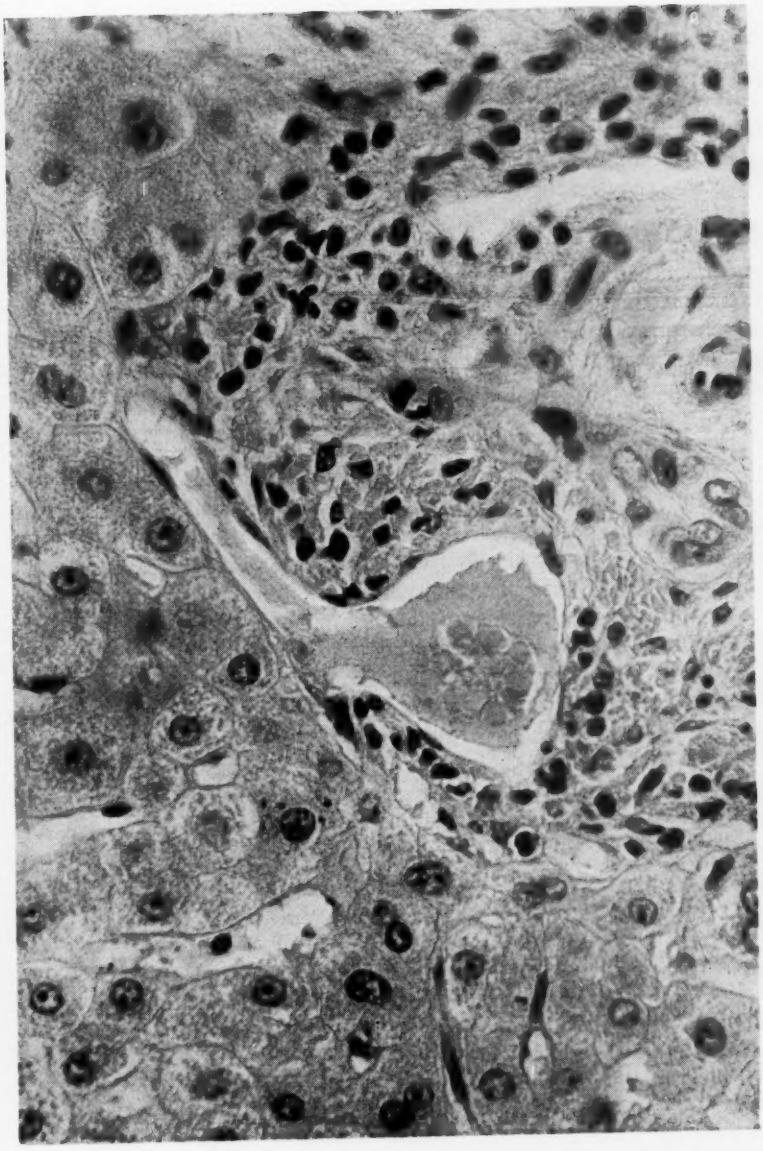

FIG. 1. *B*. Liver biopsy section of a portal triad from the same case.

The patient has felt well since, although at the end of four months total serum bilirubin was 10 mg. % and returned to normal only after eight months. We believe this to be similar to the cases due to arsphenamine reported by Gutman and Hanger.[9]

Analysis of the cases of carbarsone toxicity here reported leads us to suggest that the mechanisms may be due to:

1. *Hypersensitivity to Carbarsone:* The dermatologic toxicity cases appear to represent an allergic reaction to the arsenic. Indeed, the pathologic changes in the tissues of the fatal cases are reminiscent of the changes seen in hypersensitivity reactions in general.

2. *Overdosage:* Twenty-four of the cases, including two with central nervous system involvement, were associated with dosage in excess of our current practice. Carbarsone exerts a directly toxic effect upon tissue, and the gastrointestinal reactions appear to stem from this effect. It is believed that carbarsone dosage should not exceed 0.25 gm. three times daily for the average adult male, and twice daily for females and smaller males, and that a course should not exceed 10 days or be repeated in less than 10 days.

3. *Toxicity of the Carbarsone Preparation:* Nineteen of the cases, including the two fatalities, occurred following employment of carbarsone subsequently shown by means of a test devised by Calamari and Genn [10] to have been contaminated with arsanilic acid. The analysis as done in accordance with the United States Pharmacopoeia (14th) proved inadequate to determine toxicity. Bio-assay clearly showed toxicity. Arsanilic acid could be present in the carbarsone either by hydrolysis as a result of storage, or as a result of improper purification of the product originally. Contamination with arsanilic acid may have been a factor in some of the cases thought to have resulted from overdosage.

The cases in the literature cannot be evaluated from the standpoint of toxicity of the carbarsone preparation; however, six of the 12 were associated with dosage in excess of that here recommended (vide supra).

The exact significance of the liver damage case is not clear; however, Gutman and Hanger have suggested that this is an allergic reaction when it occurs during arsphenamine therapy. Nelson's second case appears to us to be identical with our case of liver damage except for a difference in the histologic changes which may be due to the fact that Nelson's biopsy was performed earlier in the course of the disease than was ours (15 versus 45 days). Krainer et al.,[11] in studying 19 autopsies of patients dying from acute arsenical encephalopathy during antiluetic treatments, reported that "gross acute evidence of liver or kidney damage was absent in all of the material examined. . . . Periportal round cell infiltration (of the liver) with lymphocytes, histiocytes, plasma cells and occasional eosinophilic leucocytes was a prominent and nearly constant feature." This appears to us to compare with the changes reported by Nelson, and may represent the acute process in the liver. In our case, at least, it is quite likely that this reaction should be ascribed to arsanilic acid, since it was present in the product producing the reaction.

The question of hepatic damage due to carbarsone has importance because of the frequency with which amebiasis and infectious hepatitis are associated. Of 60 consecutive admissions for infectious hepatitis, 16 (26.5%) had amebiasis, whereas amebiasis occurred 277 times (6%) in 3,999 admissions to the Tokyo Army Hospital Medical Service for all causes during the same period.[12] It is to be noted that references throughout the medical literature urge caution in the employment of carbarsone in the presence of liver dysfunction. Albright and Gordon [13] and Elsom et al.[14] noted no evident ill effects from the employment of carbarsone in treatment of amebiasis associated with infectious hepatitis. Knight and Tarun [15] were unable to demonstrate hepatic damage due to carbarsone by a battery of liver function tests. In our experience, 72 cases of concurrent infectious hepatitis, 21 cases of amebic liver abscess and 321 cases of marked amebic hepatitis were treated with carbarsone with no evidence of hepatic toxicity other than the case reported here. Comparison of the clinical course of 35 consecutive cases of infectious hepatitis with 35 consecutive cases of infectious hepatitis complicated by amebiasis which were treated with atabrine and carbarsone revealed no significant difference in the clinical course of the two groups of cases.

Close observation of patients being treated with carbarsone is mandatory. We believe the patient's best interests will be served by prompt discontinuance of the carbarsone at the least suspicion that arsenical toxicity is occurring. If the symptoms persist despite discontinuance, prompt treatment with BAL, 10% in oil, should be instituted in the doses recommended for acute arsenic toxicity.

Conclusions

1. Toxicity to carbarsone does occur. The reactions are usually heralded by gastrointestinal symptoms of epigastric burning, right upper quadrant pain and tenderness, diarrhea, nausea and vomiting, which may progress to exfoliative dermatitis, central nervous system involvement or hepatic dysfunction.

2. The mechanisms of toxicity appear to be hypersensitivity, direct effect of carbarsone on tissues usually due to overdosage, and/or toxicity of carbarsone preparation containing arsanilic acid.

3. Carbarsone is an effective adjuvant agent in antiamebic therapy and is a relatively safe form of arsenic, but due regard for proper manufacture and storage safeguards must be maintained.

4. Carbarsone should not be prescribed in excess of the dosage plan here outlined, namely, 0.25 gm. three times daily for 10 days for average sized males, and twice daily for females and smaller males. The course should not be repeated in less than 10 days after the last dose.

5. British anti-lewisite (BAL), 10% in oil, is effective in therapy of these reactions, but must be employed at the earliest sign of toxicity and in the full dose plan as recommended by the manufacturers.

ACKNOWLEDGMENTS

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SUMMARIO IN INTERLINGUA

Toxicitate a carbarsona es relativemente rar. Tamen, un revista del litteratura resultava in le discoperta de 12 casos, incluse un caso mortal, e le scrutinio del protocollos de casos al Instituto Pathologic del Fortias Armate etiam resultava in le discoperta de un caso mortal. Nostre experientia personal con toxicitate a carbarsona coperi 45 casos, duo mortal, occurrente in un serie de plus que 1500 casos de amebiasis tractate con iste droga. Le curso clinic in le casos de toxicitate face nos creder que le reaction es usualmente precedite per arditura epigastric con un sequentia rapide de dolor e sensibilitate in le quadrante abdominal dextero-superior, diarrhea, nausea, e vomito. Progression del processo usque a dermatitis exfoliative occurreva in tres casos; affection del systema nervose central in cinque; e dysfunction del systema nervose central e del hepate in un. Iste ultime caso pareva simile al intrahepatic obstruction biliari que occure in therapia antiluetic.

Le mechanismo del toxicitate pare esser (1) hypersensibilitate, (2) effecto directe de carbarsona super le tessutos, usualmente in consequentia de doses excessive, e (3) toxicitate de preparatos de carbarsona a contento de acido arsanilic. Secundo nostre interpretation, le casos de dermatitis esseva causate per hypersensibilitate al droga. Vinti-quatro del casos esseva associate con doses excedente le limites hic recommendate. In nostre opinion, le dosage de carbarsona non debe exceder 0,25 g, tres vices per die, pro le adulto mascule medie, e duo vices per die pro le adulto feminin e parve masculos, e le curso complete non debe durar plus que 10 dies. In plus, le cursos non debe esser repetite in minus que 10 dies. Dece-nove del casos reportate, incluse le duo casos mortal, occurreva post le administration de carbarsona que se revelava subsequentemente como contaminate per acido arsanilic (secundo un test elaborate per Calamari e Genn). Le analyse per le methodo recommendate per le Statounitese Pharmacopeia (14te) non esseva adequate pro determinar le toxicitate a acido arsanilic, sed bio-essayage lo monstrava clarmente.

Le casos in le litteratura non poteva esser evalutate ab le puncto de vista del toxicitate possibile del preparato de carbarsona. Tamen, sex del 12 esseva associate con dosages excedente le limites hic recommendate.

Anti-lewisite britannic, 10 pro cento in oleo per via intramuscular, es efficace in le tractamento de iste reactiones, sed illo debe esser usate al prime signos de toxicitate e in le complete plano de dosage que es recommendate per le fabricantes in casos de acute invenenamento per arsenico.

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HYPERURICEMIA ASSOCIATED WITH THE TREATMENT OF ACUTE LEUKEMIA *

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ELEVATIONS of serum and urinary concentrations of uric acid have been described in acute leukemia.[1, 2] It is also known that, with therapy, urate excretion may rise.[3, 4, 5, 6] Recently the authors have had an opportunity to view two patients who showed a marked degree of hyperuricemia concomitant with therapy of their acute lymphocytic leukemia. The authors thought that a review of these cases might point out a hazard in treating these patients.

CASE REPORTS

Case 1. A 50 year old white female housewife had been well until the winter of 1954, when she developed unusual fatigue and a low grade fever. She was admitted to the George Washington Hospital, Washington, D. C., on July 20, 1955, where hepatosplenomegaly and lymphocytosis were noted, and sternal marrow aspiration revealed acute lymphocytic leukemia. The patient received 6-mercaptopurine for three days and cortisone for 19 days, with clinical improvement. At this time she noted symptoms of a urinary tract infection and, although the urine culture was sterile, Gantrisin and penicillin were given.

The patient was referred to the National Cancer Institute on August 8, 1955, where she was found to be in clinical remission. Cortisone was gradually reduced and stopped, and the patient was discharged with no therapy.

The second admission to the National Cancer Institute was on September 2, 1955, because of clinical and hematologic relapse of her leukemia. On September 13, before the antimetabolites were started, the patient's blood chemistry, including blood urea nitrogen and uric acid, was normal. On September 14, 6-mercaptopurine, 175 mg. a day, and methotrexate, 7.5 mg. every three days, were begun, and shortly thereafter the patient became nauseated and vomited. After six days of antimetabolite therapy, repeated tests revealed a blood urea nitrogen of 119 mg.%; uric acid, 34.8 mg.%; CO_2, 14 mEq./L.; chlorides, 96 mEq./L.; sodium, 119 mEq./L.; potassium, 7.0 mEq./L. The white blood cell count fell from 6,600 with a few abnormal forms to 1,600 with no abnormal forms, while the platelets fell from 127,500 to 15,000 by September 19. Antimetabolites were immediately stopped and, after 11 days of supportive therapy plus cortisone and hydrocortisone, all the blood chemical determinations had returned to normal (figure 1). The renal functional status prior to discharge was as follows: A phenolsulfonphthalein test showed 16% excretion in 15 minutes and 38% excretion in one hour. Urinary specific gravity was fixed at 1.011. At the time of discharge the patient was in a complete hematologic remission.

The patient's third admission, from October 25, 1955 to December 29, 1955, was precipitated by another clinical and hematologic relapse. Treatment consisted of 19 days of Meticorten, without alteration of the disease but with a rise in the blood urea

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nitrogen to 29 mg.%. Next methotrexate, 2.5 mg. a day, and 6-mercaptopurine, 150 mg. a day, were given for six days and stopped because of persistently elevated blood methotrexate levels. Shortly thereafter a 16-day course of 6-mercaptopurine, 150 mg. a day, and methotrexate, 7.5 mg. every three days, was administered, after which the bone marrow showed virtually complete remission. No renal complications similar to that noted on the second admission ensued, and prior to the patient's discharge her phenolsulfonphthalein excretion was 29% in 15 minutes and 66% in two hours. Urine concentration test showed a specific gravity of 1.013, and urinalysis was otherwise normal. The patient was discharged on small maintenance doses of 6-mercaptopurine and methotrexate.

Improvement continued until January 6, 1956, when blast forms appeared in the peripheral blood. At this time the patient had an episode of acute pyelonephritis,

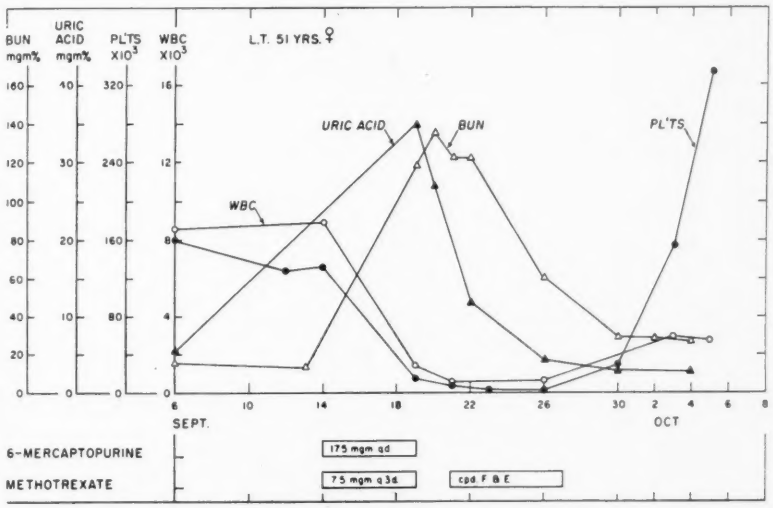

FIG. 1. *Case 1.* Note the rapid fall in the white blood cell count and platelet count that occurred simultaneously with elevations of serum uric acid and blood urea nitrogen values.

which was successfully treated with tetracycline. On January 27 the white blood count had risen to 140,000, with 75% abnormal forms; the platelets had fallen to 24,000; blood urea nitrogen was 17 mg.%, and serum uric acid was 9.8 mg.%. The patient was re-admitted, the antimetabolites were stopped, and hydrocortisone, 200 mg. a day, was begun. On admission the patient had eructation and singultus and was alternately lethargic and agitated. Three days after hydrocortisone was started the blood urea nitrogen had risen to 114 mg.%, uric acid to 43 mg.%; creatinine was 6.8 mg.%; CO_2, 17 mEq./L.; chlorides, 97 mEq./L.; sodium, 134 mEq./L.; calcium, 8.1 mg.%; phosphorus, 21.9 mg.%. Concomitantly, the white count fell to 1,500, with no abnormal forms, and the platelets decreased still further (figure 2). It became apparent that the patient was again having an "acute uremic episode" similar to that on her second admission. Conservative treatment to clear the metabolic load imposed upon the kidneys was undertaken, and on this therapy the blood urea nitrogen gradually fell to 68 mg.%, uric acid fell to a low of 8.8 mg.%, and the creatinine to 2.8 mg.%.

The hydrocortisone was continued at a reduced level of 75 to 100 mg. a day

throughout this episode. On February 4, 1956, the patient had a severe shaking chill, and hemolytic *Staphylococcus aureus* was cultured from the blood. This was treated successfully with massive doses of penicillin and tetracycline plus streptomycin. On February 9 the patient became hypotensive, and refractory to the administration of whole blood and norepinephrine.' Coffee-ground material and bright red blood were obtained from the stomach, and massive ecchymoses appeared over the entire body. Despite blood replacement, the patient died shortly thereafter.

Autopsy revealed generalized leukemic infiltration of all organs and moderate leukemic infiltration of the kidneys. Hemorrhagic areas were noted in all organs, and several hundred milliliters of fresh blood were found in the gastrointestinal tract. Doubly refractive crystals were seen in the kidney sections. On Galantha stain these were shown to be urate crystals. Chemical analysis of the renal tissue, carried out by Dr. James S. Wyngaarden, of the National Institute of Arthritis and Metabolic Diseases, revealed high uric acid content. This determination was carried out by

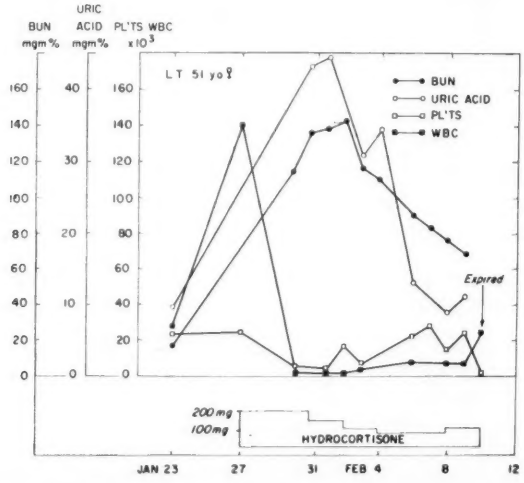

FIG. 2. *Case 1.* Here, one sees the rapid elevation of white blood cell count, signifying rapid production of malignant tissue, followed by a precipitous fall associated with rises in serum uric acid and blood urea nitrogen values.

hydrochloric acid and lithium carbonate extraction of fresh frozen kidney tissue. The pyramid area contained 0.7 μg of uric acid per milligram of dried defatted tissue, and the cortical area contained 0.04 μg of uric acid per milligram of tissue. No uric acid was found in a control kidney.

Case 2. This patient was an eight year old white male whose present illness started in March 1956 with nausea, vomiting and dehydration. At this time his white cell count was 10,200, with a normal differential. The patient recovered and was well for sevaral days, but then complained of headache and leg pain, and ran a low grade fever. On March 22 the child appeared pale and underweight, and a hematologic review showed a hemoglobin of 11.2 gm. and a white blood cell count of 16,200. One week later his hemoglobin was 10.2 gm.; white blood cell count, 17,900, with 73% lymphocytes, 26% polymorphonuclears, and 1% monocytes.

The patient's condition grew worse and he was admitted to the hospital on April 1, where he appeared acutely ill, pale and dehydrated. Hepatosplenomegaly was noted.

Hemoglobin was 7.7 gm.; white blood cell count, 26,900, with mostly blasts seen on smear. Urinalysis showed 4 plus albuminuria, and electrolytes were normal. On April 2 the patient was begun on ACTH-gel, 50 units every six hours, and on April 4 both 6-mercaptopurine, 75 mg. a day, and cortisone, 10 mg. every six hours, were started. One week later the patient was transferred to the National Cancer Institute.

There was no history of previous renal disease. Easy bruisability and bleeding from needle puncture sites had been noted during the last month.

Admission physical examination revealed a lethargic, pale, malnourished and acutely ill patient. The facial contour was rounded and the breath malodorous. Ecchymoses were noted at needle puncture sites. Hemorrhages, leukemic infiltrations and minimal papilledema were seen in the optic fundi. Abdominal distention, hepatosplenomegaly and hyporeflexia were noted.

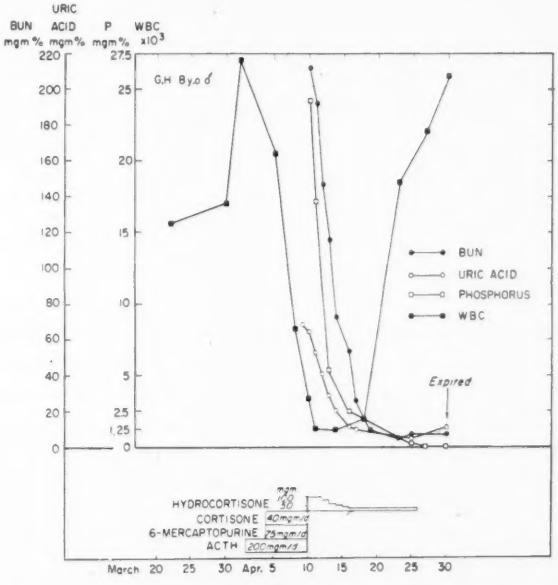

FIG. 3. *Case 2.* Note changes of white blood cell counts, serum uric acid and blood urea nitrogen determinations similar to those seen in the previous case. Also shown are the serum phosphorus levels explained in the text. No blood chemistry values prior to therapy are available.

The laboratory data were as follows: urinalysis, negative except for many red cells on microscopic examination; white blood cell count, 3,400, with 70% lymphocytes, some being abnormal forms; hemoglobin, 8.1 gm.; platelets, 4,500; blood urea nitrogen, 212 mg.%; uric acid, 68.2 mg.%; creatinine, 3.2 mg.%; phosphorus, 24.2 mg.%; calcium, 4.6 mg.%; potassium, 7.5 mEq./L.; CO_2, 7 mEq./L.; sodium, 127 mEq./L.; chlorides, 92 mEq./L.; alkaline phosphatase, 3.4 Bodansky units; blood sugar and liver function studies, normal.

Because of the patient's critical condition the previous medications were stopped and hydrocortisone, 25 mg. every six hours, and parenteral fluids were started. Despite correction of electrolyte imbalance the patient's stuporous state continued. On April 11 a few vesicular and pustular lesions appeared on his skin, from which

hemolytic *Staphylococcus aureus* was cultured. These regressed under local therapy. Clinically the patient appeared to be improving, but the papilledema steadily increased. On April 14 the blood urea nitrogen had dropped to 72 mg.% and the uric acid to 20 mg.%. During the next two days the patient was febrile, and blood cultures revealed the presence of hemolytic *S. aureus*. Penicillin, streptomycin and later erythromycin were used to combat this infection. The fever subsided during the following two days, and by this time electrolytes and other blood chemistry values (figure 3) were nearing normal limits. By April 22 the patient had improved and was taking fluids by mouth. Three days later the blood urea nitrogen was 7 mg.%; uric acid, 5.6 mg.%; phenolsulfonphthalein excretion, 56% in 30 minutes and 82% in two hours. Skull films showed spreading of the sutures, indicating increased intracranial pressure. Irregular respirations resembling Cheyne-Stokes breathing were observed and continued throughout the rest of the patient's course. Increasing hepatosplenomegaly was noted, and a bone marrow aspiration revealed the presence of many abnormal, immature lymphocytic cells. On April 26 the serum phosphorus was 0.2 mg.%; calcium, 7.4 mg.%; alkaline phosphatase, 24.2 Bodansky units. Vitamin D and calcium were started, with no apparent benefit. In the last few days the patient exhibited signs of progressive increasing intracranial pressure, and died on April 30.

Autopsy revealed leukemic infiltration of all organs, with marked leukemic involvement of the liver and kidneys, with many small hemorrhages. No uric acid crystals were noted in the kidneys, and these organs were not studied for uric acid content. No hydrocephalus was seen, but leukemic infiltration of the meninges was present.

Discussion

In the first patient reported, hyperuricemia was related to the administration of 6-mercaptopurine and methotrexate (amethopterin) on one occasion, and of hydrocortisone during the second episode. In the second patient, hyperuricemia occurred concomitant with the administration of 6-mercaptopurine, cortisone and ACTH.

Marked rise in serum uric acid and excretion of uric acid following antileukemic treatment may be explained by the following hypotheses: (1) The drugs may actually cause lysis of the leukemic cells in the blood, bone marrow and other tissues, and release large amounts of nitrogenous products and uric acid, causing an "acute uremic" picture. (2) Large amounts of uric acid and other purines and pyrimidines may of themselves interfere with normal renal function. It has been shown that adenine causes a uremic picture due to deposition of 2,8-dioxyadenine in the kidneys.[7] (3) Chemotherapeutic agents may interfere with the re-utilization of nucleic acid breakdown products derived from white blood cells. Preëxisting renal disease or leukemic infiltration of the kidney may aggravate the magnitude of the metabolic charges.

In case 2 the precipitous fall in serum phosphorus, while it paralleled the fall in serum uric acid and blood urea nitrogen, continued to extremely low levels while the urinary excretion also fell. This could possibly be explained by a rapid build-up of malignant tissue following the tapering of the dose of hydrocortisone, as evidenced by a rapid rise in the white blood cell count from 2,000 to 18,000 in three days and the increase in organomegaly.

Previously Burchenal [8] had observed that folic acid antagonists are not excreted normally if renal function is poor. In case 1 we too observed this phenomenon.

Rise in uric acid after treatment of leukemia has been observed for some years. Jugenburg and Tschotschia [3] in 1931, in irradiating cases of chronic leukemia, were aware of the dangers in a rise of serum uric acid concomitant with decrease in leukemic tissue. Merrill [4] reported three cases of chronic leukemia in which renal failure was accentuated apparently by x-ray therapy. Bedrna and Polcak [5] have reported two cases of chronic leukemia with acute ureteral obstruction by uric acid stones following x-ray therapy. Sandberg, Cartwright and Wintrobe [9] studied uric acid excretion in 38 cases of leukemia before, during and after chemotherapy. The uric acid excretion in normals was 6.5 mg./kg./24 hrs. In untreated acute lymphocytic leukemia the mean value of uric acid excretion in the urine was 30.2 mg./kg./24 hrs., while in acute myelocytic leukemia, chronic myelocytic and chronic lymphocytic leukemia, uric acid excretion was less than 14 mg./kg./24 hrs. In treated acute lymphocytic and acute myelocytic as well as one case of chronic myelocytic leukemia, a further rise in the already elevated urine uric acid was noted. Cortisone, 6-mercaptopurine and methotrexate all were capable of increasing uric acid excretion. In case 1 the uric acid excretion after treatment varied from 8.7 mg./kg./24 hrs. to 37.1 mg./kg./24 hrs., while in case 2 the range after treatment was from 17.7 mg./kg./24 hrs. to 81.6 mg./kg./24 hrs. No determination of the amount excreted before treatment was obtained.

In every case of acute leukemia the possibility of an acute uremic episode concomitant with antileukemic therapy should be considered. The risk is apparently greatest in patients with acute lymphocytic leukemia with a high white blood count. The following plan is suggested to ameliorate or prevent such an occurrence:

1. Obtain urinalysis, blood urea nitrogen and uric acid determinations prior to therapy. If these are abnormal, further evaluation of renal status should be undertaken.
2. Force fluids during treatment if marked uricosuria is present, and administer alkali by mouth to prevent precipitation of uric acid crystals.
3. Observe closely the levels of serum uric acid during treatment.

Summary

Three episodes of hyperuricemia and uremia secondary to antimetabolite and steroid therapy of acute lymphocytic leukemia have been presented. The pertinent literature relative to this problem has been reviewed, and suggestions as to prevention and treatment have been made.

Acknowledgment

We wish to extend our appreciation to Dr. James S. Wyngaarden, Dr. Alan S. Rabson, Dr. Louis B. Thomas, Dr. Thomas J. Kennedy, Jr., and Dr. Emil Frei for their coöperation and assistance.

SUMMARIO IN INTERLINGUA

Es presentate tres episodios de hyperuricemia e uremia associate con le tractamento de acute leucemia lymphocytic. In le prime episodio, hyperuricemia occurreva in concomitantia con le administration de 6-mercaptopurina e methotrexato; in le secunde, con le administration de hydrocortisona; in le tertie, que esseva un episodio de hyperuricemia e de uremia, con 6-mercaptopurina, cortisona, e ACTH.

Le marcate augmento del acido uric in le sero e del excretion de acido uric post tractamentos antileucemic pote esser explicate per le sequente hypotheses: (1) Le droga de facto causarea lyse de tessuto, liberante grande quantitates de productos nitrogenose e de acido uric con le effecto del presentation de un tableau de uremia "acute." (2) Grande quantitates de acido uric e de altere purinas e pyrimidinas obstruerea per se le functionamento normal del renes. Il ha essite demonstrate que adenina effectua un stato uremic como resultato del deposition de 2,8-dioxyadenina in le renes. (3) Agentes chimotherapeutic obstruerea le re-utilisation de productos de decomposition de acido nucleic de origine leucocytic. Le pre-existentia de morbo renal o de infiltrationes leucemic del renes pote aggravar le magnitude del alterationes metabolic.

In omne caso de leucemia acute on debe contar con iste possibilitate que acute episodios uremic se declara in concomitantia con le therapia antileucemic. Il pare que le risco es plus grande in patientes con acute leucemia lymphocytic qui ha un alte numeration leucocytic. Le sequente plano es proponite pro meliorar o prevenir le occurrentia de tal episodios:

1. Obtener urinanalyses e determinationes del contento sanguinee de nitrogeno de urea e de acido uric ante le institution del therapia. Si le resultatos es non normal, evalutationes additional del stato renal es a interprender.

2. Fortiar fluidos durante le tractamento in caso de marcate grados de uricosuria, e administrar alcali per via oral pro prevenir le precipitation de crystallos de acido uric.

3. Scrutinar le nivellos seral de acido uric durante le tractamento.

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SPOROTRICHOSIS: A REPORT OF 12 CASES, INCLUDING TWO WITH SKELETAL INVOLVEMENT *

By W. M. Mikkelsen, R. L. Brandt and E. R. Harrell,
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Sporotrichosis is a subacute or chronic infection caused by *Sporotrichum schenckii* and usually limited to the skin and subcutaneous tissue. However, since extracutaneous dissemination may occur, the disease should be grouped with the deep mycoses. Sporotrichosis has been reported from all continents and occurs without regard for sex, age or race. Although several species of Sporotrichum have been described, the presently prevailing opinion is that only one, *S. schenckii,* is pathogenic to man.[1] This organism occurs as a saprophyte on various plants, shrubs, flowers, fruits and vegetables and has been isolated from soil. Infection has been demonstrated in a number of wild and domesticated animals and in insects. Human infection is usually the result of inoculation of an injured area of skin, although such a history is frequently lacking in systemic or extracutaneous forms. Direct person-to-person transmission probably does not occur, although infection has followed the handling of bandages from clinical lesions. Laboratory infections have been reported. So many cases have occurred in farmers, gardeners and florists that Foerster [2] has termed sporotrichosis an occupational disease. An incredible "epidemic" has been reported in which more than 2,800 cases resulted from exposure to infected timbers in the gold mines of South Africa.[3]

Clinical Features

A modified clinical classification of the disease is given in table 1. The great majority of cases are of the localized lymphangitic type. Typically, there is a history of minor trauma (i.e., a scratch or prick with a thorn or sliver, an insect bite, etc.), followed within one to four weeks by the appearance of a small, painless papule or pustule. As a rule this primary sore enlarges, breaks down and forms an ulcerated, chancre-like lesion. Within several weeks to several months a series of subcutaneous nodules develops along the path of lymphatic drainage of the primary lesion. There may be a cordlike thickening of the lymphatic vessels between the nodules. The

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nodules may soften and ulcerate. Regional lymphadenopathy is seldom prominent. The process remains localized to the involved extremity, and systemic symptoms are conspicuous by their absence. Spontaneous healing is rarely observed.

In the fixed cutaneous form the process is restricted to the site of inoculation. There is local enlargement which may be verrucous in character, or which may simulate cutaneous carcinoma, acne or a number of granulomatous processes.

In some instances the organism is disseminated via the blood stream. Multiple nodules may appear over the entire body surface, or there may be only a few scattered lesions. These nodules may remain indurated or may soften centrally, forming an abscess which may finally discharge to form an ulcer with a firm, erythematous margin. Such patients may display marked fever and other systemic symptoms and, unless treated, may pursue an abrupt downhill course and die.

The occurrence of allergic "id" lesions has been reported by Young and associates.[4]

TABLE 1

Cutaneous forms
Localized lymphangitic
Fixed cutaneous
Hematogenous cutaneous
Sporotrichids
Extracutaneous forms
Mucous membranes
Bone, synovium, tendinous structures and muscle
Ocular
Visceral (systemic)
Lung, GI tract, CNS—very rare

The extracutaneous or systemic forms may occur secondary to the cutaneous forms, or in their absence. Lesions of the mucous membranes of the nose, mouth and pharynx have been noted. Involvement of the musculoskeletal system has frequently been reported in the French literature,[5, 6, 7, 8] although it is considered less common in the United States.[9, 10, 11] Gougerot[11] in particular has stressed "the singular frequency of lesions in the bones, which is about 10 per cent in disseminated sporotrichoses."

Ocular lesions may involve the conjunctivae, eyelids, cornea or entire globe.[12] Occasional fulminating fatal cases with lesions demonstrable in many internal organs have been reported.[13] Pulmonary,[14] gastrointestinal[15] and central nervous system involvement[16] is very rare.

DIAGNOSIS

The clinical picture in the localized lymphangitic type is highly suggestive of the diagnosis. The diagnosis is easily confirmed by culture, since

the organism grows readily on Sabouraud's glucose agar. Growth is biphasic (figure 1). At room temperature a small white colony is visible within a few days. Within a few weeks this becomes a wrinkled, jet-black colony. With repeated subculturing the color may fade to a brown or gray. Microscopic examination of material from the colony grown at room temperature reveals a mycelial growth with delicate, branching, septate hyphae and clusters of round, oval or pyriform microconidia which are loosely attached to the lateral branching conidiophores (figure 2). At 37° C. a

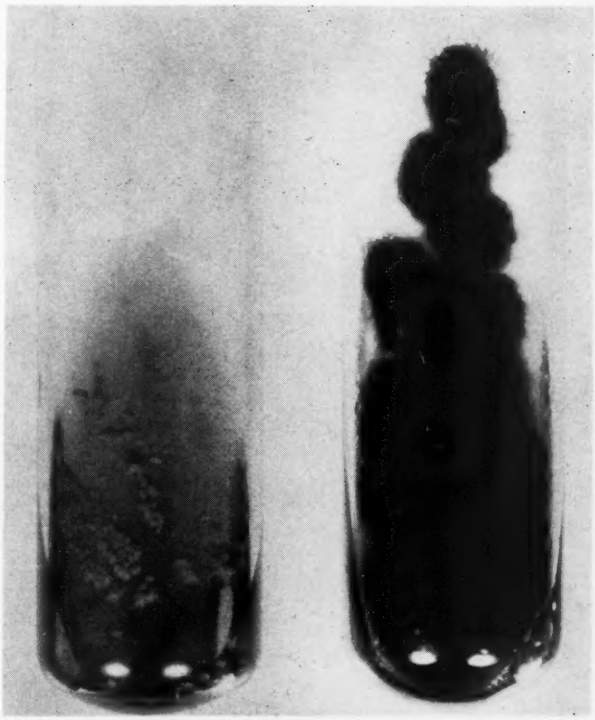

FIG. 1. Cultures of *Sporotrichum schenckii;* yeast phase (37° C.) on the left and mycelial phase (room temperature) on the right.

moist white or grayish white colony appears. Microscopic examination reveals round, oval or elongated structures which frequently exhibit budding (figure 3). By subculturing at the appropriate temperature, growth can be converted from the mycelial to the yeast phase and back again.

The diagnosis can be further substantiated by the intraperitoneal injection of a mouse or rat with material from the colony and subsequent demonstration of gram-positive, cigar-shaped organisms in smears from infected testis, lymph node or spleen (figure 4).

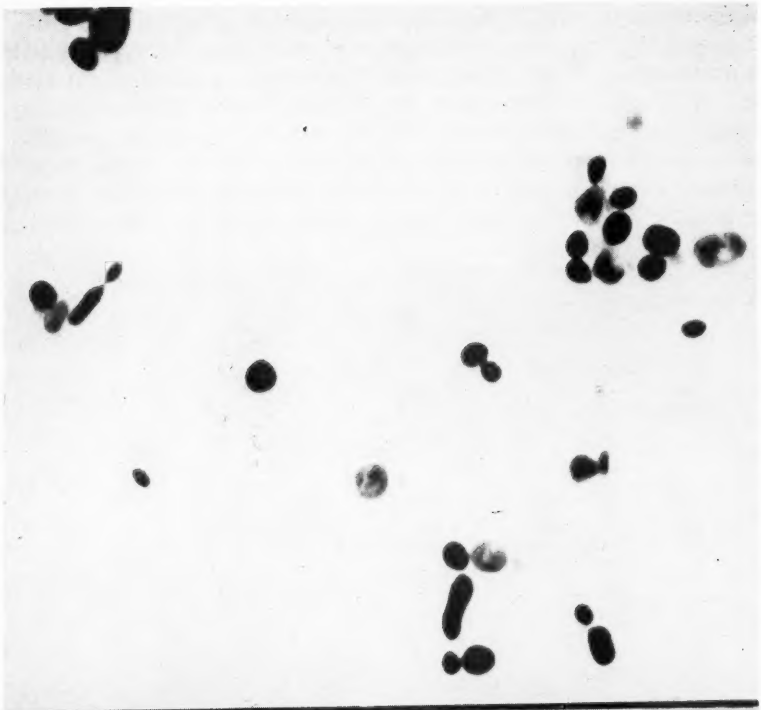

FIG. 3. Microscopic appearance of yeast phase, showing numerous gram-positive organisms, some of which exhibit budding.

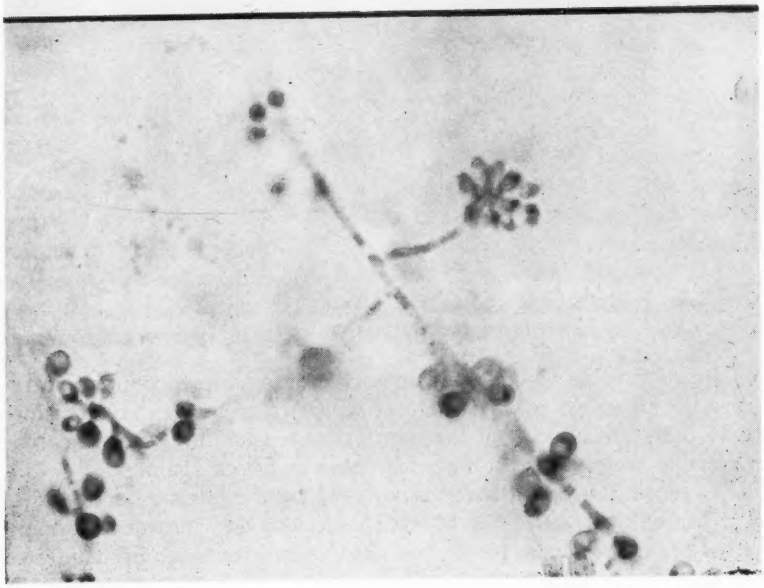

FIG. 2. Microscopic appearance of mycelial phase.

The organism has only rarely been demonstrated in fresh preparations of material from the skin lesions or in sections of tissue obtained by biopsy. Lawless [17] has described a method of hanging-drop culture which should increase the diagnostic value of fresh preparations. The use of modifications of the periodic acid Schiff staining procedure, which stains the polysaccharide capsular substances of all the fungi, greatly increases the likelihood of demonstrating the organism in tissue sections.[18]

The histologic appearance of the lesions is that of a nonspecific granulomatous process with central necrosis and surrounding polymorphonuclear

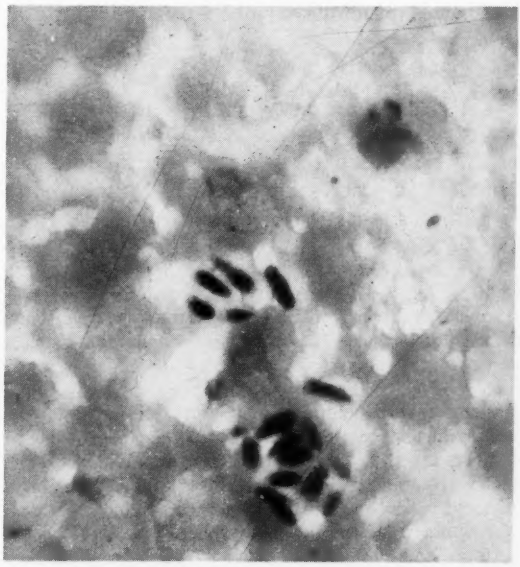

FIG. 4. Smear of macerated lymph node from a rat injected intraperitoneally with yeast phase material isolated from case 9.

leukocytes and foreign-body giant cells. As noted above, the organisms may occasionally be demonstrable. More rarely the so-called "asteroid bodies," consisting of round, thick-walled cells with surrounding club-shaped radiations, are visualized.[19, 20]

A sporotrichin skin test, utilizing material prepared from the yeast phase, is reported to show little cross reaction with cutaneous tests for other fungous infection.[21] A positive skin reaction has essentially the same significance as a positive tuberculin skin test in tuberculosis. Agglutinins, precipitins and complement-fixing antibodies may develop in response to infection, but are of little clinical value.

Therapy

Iodide therapy may be regarded as specific. A saturated solution of potassium iodide is started in a dose of five drops three times daily and increased by one drop daily to 35 or 50 drops three times daily, or to tolerance. Clinical response is not immediate, but is usually evident within several weeks. Therapy should be continued for at least a month beyond the point of apparent healing in order to prevent relapses. In the event iodide therapy cannot be used, stilbamidine [22] or 2-hydroxystilbamidine [23, 24] should be tried. Roentgen therapy has been considered of some value as a therapeutic adjunct, especially in cases of the localized lymphangitic type. Sulfa drugs, penicillin and the newer antibiotics are of no value, except in the control of secondary infection.

Case Reports

A total of 12 cases of sporotrichosis have been seen at the University of Michigan Hospital. No cases were diagnosed prior to 1940, and only two cases prior to 1950. With increasing awareness of the frequency of mycotic disease and the routine application of cultural technics, 10 cases have been encountered since 1950.

Case 1. A nine year old boy was first seen on August 13, 1940. Three weeks earlier he had observed a "sliver" in the left index finger. The site became swollen and red, and gradually enlarged. Hot compresses and local roentgen therapy were ineffective. Three nodular lesions appeared on the medial aspect of the left forearm and the patient was referred to the University of Michigan Hospital.

Physical examination revealed a granulomatous lesion, 2 by 2 cm., on the dorsum of the left index finger. There was a central crater within which pus was visible. Along the lymphatic channels of the left upper extremity were a series of eight lima bean-sized subcutaneous nodules. Left epitrochlear and axillary nodes were palpable. The remainder of the physical examination was essentially negative.

Iodide therapy was started, and on August 26 and September 3 the patient received 75 r in air to the lesion on the left index finger and to the subcutaneous nodules. By September 10 there was striking improvement, and by October 8 the subcutaneous nodules had disappeared and involution of the primary finger lesion was virtually complete.

Case 2. A 15 year old girl was seen on October 10, 1950. About August 1 she had had a mosquito bite on the right wrist. The following day she visited a farm where she pitched hay and went horseback riding. Approximately two weeks later a crusted papular lesion appeared at the site of the original mosquito bite. After another two weeks a series of painless subcutaneous nodules appeared along the flexor aspect of the right arm. Penicillin, sulfonamides and Aureomycin were administered, without significant benefit.

Physical examination revealed a fungating lesion, 1.5 by 2.5 cm., with a raised border and a yellow-red granulating base, on the ulnar aspect of the right wrist. Several subcutaneous nodules, approximately 2 cm. in diameter, were present along the flexor aspect of the right forearm and upper arm. These were freely movable, although the overlying skin was erythematous. Several pea-sized lymph nodes were palpable in the right axilla.

Material from the primary lesion on the right wrist yielded a growth of *S. schenckii*.

On October 12 iodide therapy was instituted. By October 20 the primary lesion appeared less exudative and the subcutaneous nodules were less indurated. By December 1 all lesions were virtually healed, and on December 22 there was only a residual scar at the site of the original lesion.

Case 3. A two and one-half year old boy was first seen on June 20, 1951. Ten days earlier his mother had noticed a mosquito bite on the ulnar aspect of the right wrist. This gradually enlarged and the surrounding skin became erythematous.

Physical examination revealed a smooth, firm swelling, 1 by 2 cm., on the ulnar aspect of the right wrist. This was nonfluctuant, unattached to bone or tendon, and appeared to lie in the deep subcutaneous tissue.

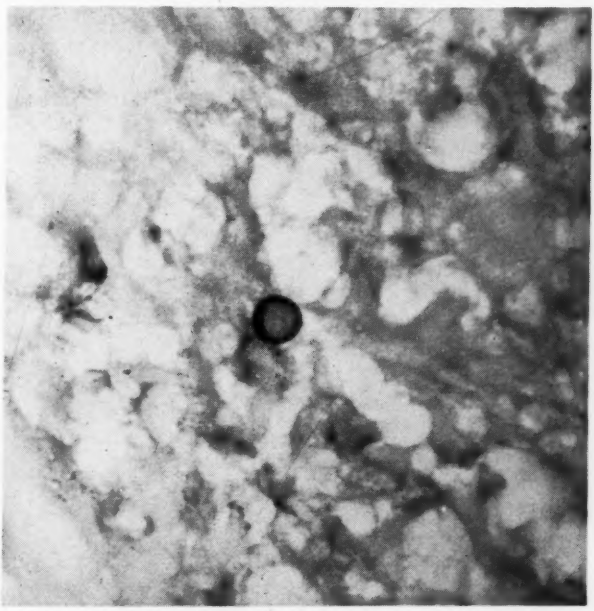

FIG. 5. *Case 3.* Biopsy of granulomatous lesion on the right wrist. Section stained by the Hotchkiss-McManus modification of the periodic acid Schiff technic. Many round and oval Schiff-positive bodies, thought to represent the organism, were seen.

Laboratory studies were negative except for a white blood cell count of 13,400 per cubic millimeter. On June 21 the lesion was biopsied. Histologic examination revealed a granuloma containing individual nodules epithelioid in character and relatively avascular. It was considered more suggestive of tuberculosis than of any other of the specific granulomas. The Hotchkiss-McManus modification of the periodic acid Schiff stain later revealed numerous round and oval Schiff-positive bodies characteristic of the tissue forms of *S. schenckii* (figure 5). On July 9 the site of the wound appeared as a granulomatous ulcer, and proximally, along the path of lymphatic drainage, there had appeared a series of four freely movable subcutaneous nodules, each 2 to 3 mm. in diameter. Lymph nodes were readily palpable in the right axilla.

Material obtained for culture at this time produced a growth of *S. schenckii*. Agglutinations for tularemia were negative. Tuberculin skin tests were negative in 1 : 1,000 and 1 : 100 dilutions.

On July 23 iodide therapy was started. There was gradual but progressive healing.

Case 4. A 40 year old housewife was first seen on August 30, 1951. Six weeks previously, while working with her raspberry bushes, she had scratched her right elbow. A week later a small papulopustular lesion appeared at the site of the scratch. This gradually enlarged and ulcerated. About three weeks after the original injury

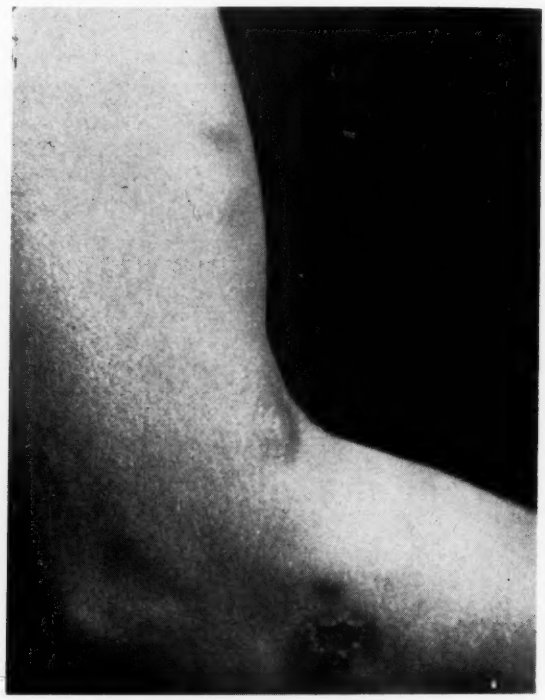

FIG. 6. *Case 4.* Typical localized lymphangitic type showing the ulcerated primary lesion with a series of subcutaneous nodules along the lymphatic pathway.

a series of firm, painless nodules appeared in the upper arm along the course of lymphatic drainage. There were no systemic symptoms. Penicillin and sulfa drugs were administered without benefit.

Physical examination revealed a granulomatous ulcerating lesion from which pus could be expressed, located on the radial aspect of the right forearm just distal to the elbow. Extending up the anterolateral aspect of the upper arm were five firm subcutaneous nodules (figure 6).

Direct examination of material obtained from the primary lesion was negative for fungi. On culture, however, *S. schenckii* grew readily. Following oral administration of a 1 mc. dose of radioiodine, no increased uptake could be demonstrated by external counting over the lesions.

Iodide therapy, started on September 7, resulted in prompt healing.

Case 5. An 18 year old student was first seen on June 26, 1952. Six weeks earlier he had discovered what was thought to be a "sliver" in the left index finger. Local swelling and erythema progressed despite parenteral and local antibiotics.

Physical examination revealed a small papular lesion over the central portion of the distal phalanx of the left index finger. This had been previously incised and was discharging a seropurulent material which on direct examination revealed no fungi. This was thought to be a bacterial infection, and Neomycin ointment was prescribed.

By July 11 the wound had partially healed. However, a series of nodules was observed along the lymphatic channels of the left forearm. These were deep-seated, nontender and movable. The overlying skin was erythematous. One of the nodules was fluctuant, but none had ulcerated. Pus aspirated from one of these lesions produced an abundant growth of *S. schenckii.* Therapy consisted of stilbamidine, 150 mg. in normal saline intravenously three times weekly for a total of six injections, or 0.9 gm. There was no untoward reaction to this medication, and the lesions were virtually healed by the time the course of therapy was complete. A check-up eight months later revealed no recurrence. This case has been previously reported by Harrell and associates.[22]

Comments: The preceding five cases are classic examples of the localized lymphangitic type of infection. In each there was a history of minor trauma, followed within several weeks by the appearance of a primary papular lesion. Typical subcutaneous nodules appeared along the path of lymphatic drainage two to three weeks later. Diagnosis was confirmed by culture in each case and by biopsy in case 3. Some degree of regional lymphadenopathy was present in three of the five cases. Local and systemic antibiotics were administered in cases 2, 4 and 5, without appreciable benefit. The first four cases were treated with potassium iodide, with complete healing and without recurrence. Case 5 received 0.9 gm. of stilbamidine intravenously during a two-week period, with complete healing within one month.

Case 6. A two year old boy was admitted on December 1, 1952. Four weeks previously his mother had noted a pimple on his forehead. She stated that the child had a habit of rubbing his forehead on the rug. A week later the lesion enlarged and a purulent discharge appeared. Parenteral penicillin and local antibiotic ointments resulted in some decrease in erythema and discharge, but the lesion continued to enlarge and ulcerate.

On physical examination there was a midline ulcer on the forehead, 1.5 cm. in diameter and 0.5 cm. in depth. There were a red granular base and a raised border. On the bridge and right side of the nose were two fluctuant, deep nodules, 0.5 cm. in diameter, with a bluish purple discoloration of the overlying skin (figure 7). There was no significant adenopathy. The remainder of the physical examination was essentially negative. Routine laboratory studies were essentially negative except for an eosinophilia of 21%.

A tuberculin skin test was negative in 1:10,000 dilution. A biopsy of the lesion revealed inflammatory granulation tissue without recognizable characteristics; no causative organisms could be identified with special staining. Four consecutive cultures of purulent material from the forehead lesion yielded profuse growth of *S. schenckii.* Material from a culture was injected into a white rat on December 11, 1952. The animal died 26 days later and the organisms were recovered from the testes.

Iodide therapy was started on December 15. By April 15, 1953, the lesion was healed and therapy was discontinued. On examination nearly three years later there was a slightly depressed, atrophic scar without evidence of reactivation.

Comments: This case also represents an example of the localized lymphangitic type. The unusual location was attributed to the child's habit of rubbing his forehead on the rug. The diagnosis was established by cultural methods. There was a prompt and complete response to iodide therapy.

Case 7. An 11 year old schoolgirl was first seen on October 15, 1953. Three weeks earlier, and two weeks following dental repair, an erythematous papule appeared over the midportion of the right mandible. This gradually enlarged and at the time of examination appeared as an erythematous, indurated area measuring 3 by 8 cm. There was a central area of ulceration and granulation tissue, 1 by 4 cm., from which sanguinopurulent material exuded (figure 8). An indurated nodule, 1 cm. in

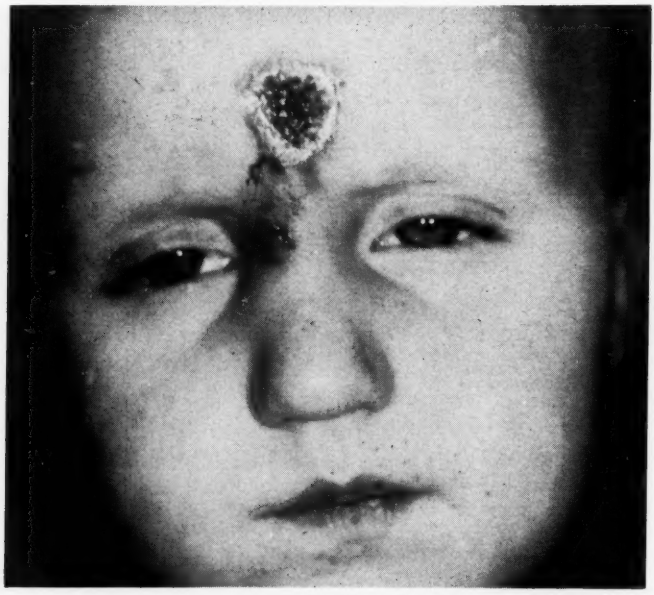

FIG. 7. *Case 6.* An unusual example of the localized lymphangitic type.

diameter, was palpable in the submental area. The remainder of the physical examination was essentially negative.

A biopsy of the lesion revealed papillomatous hyperplasia of the stratified squamous epithelium, with small abscesses in and beneath the epidermis. The causative organisms could not be demonstrated in routine sections or those stained by the periodic acid-Schiff method. On Sabouraud's medium an abundant growth of *S. schenckii* was evident within a week. Iodide therapy was started on October 26, 1953. By December 30 healing was virtually complete. Iodide therapy was continued for an additional six weeks and then discontinued. On March 19, 1954, there was a somewhat hypertrophic scar but no evidence of reactivity.

Case 8. A 47 year old farmer was first seen on January 6, 1956. In October, 1955, a small erythematous nodule had appeared on the neck just to the right of the thyroid cartilage. It had become pustular, and the patient's wife had probed the area,

believing he had an ingrown hair. A small amount of purulent material appeared. Within several days two additional cherry-sized nodules developed, one in the midline anteriorly and the other at the angle of the right mandible. There were no systemic symptoms, and the patient could recall no previous trauma or injury to the face or neck. A short time before the cutaneous lesions had appeared the patient had noted a small, tender ulceration on the lower right gum at the base of the lateral incisor. One of the patient's cows had had mastitis and an associated erythematous eruption with several nodules on the udder. Prior to being seen the patient had received penicillin, roentgen therapy and ammoniated mercury ointment locally, all without benefit.

Physical examination was essentially negative except for the presence on the neck of three nodules, each approximately 2 cm. in diameter and crusted centrally. These were located at the angle of the right mandible, in the midline over the larynx and midway between the sternocleidomastoid muscle and the thyroid cartilage.

FIG. 8. *Case 7.* Sporotrichosis clinically resembling actinomycosis.

The clinical impression was cervicofacial actinomycosis. The lesions were incised and a gelatinous purulent material was easily expressed. Direct examination for sulfur granules was negative. Cultures were made. The patient was placed on Aureomycin, 500 mg. four times daily.

No improvement was noted when he returned two weeks later. By that time the cultures had produced a growth of *S. schenckii,* and the patient was hospitalized for a course of therapy with 2-hydroxystilbamidine. The physical examination was unchanged. Routine blood and urine examinations were within normal limits. The total serum protein was 7.7 gm. %, with albumin 4.7 and globulin 3.0. X-ray examination of the chest was negative.

In a five-day period the patient was given 2,100 mg. of 2-hydroxystilbamidine intravenously. Mild nausea, vomiting and diarrhea were present on the second day but did not persist or recur, despite continuation of therapy. There was no significant change in blood values during this period. At the time of discharge, immediately following the five days of treatment, there was a slight but definite decrease in size of the lesions. When seen later the lesions were completely healed.

Comment: Cases 7 and 8 are likewise examples of the localized lymphangitic type. Clinically these cases closely resembled actinomycosis, and the correct diagnosis was established by cultural methods. In case 7 iodide therapy was successful. In case 8, 2-hydroxystilbamidine was administered, with resultant cure.

Case 9. A 63 year old farmer was seen on March 1, 1951. In October, 1949, during the corn husking season, he had noted an area of erythema on the dorsum of the left wrist. Within a few days several papulovesicular lesions appeared at this site. A weeping surface developed, and the process spread peripherally to involve all of the wrist except the volar surface.

FIG. 9. *Case 8.* Fixed cutaneous lesion of sporotrichosis present for 17 months without spread.

Physical examination revealed an oval lesion, 2 by 4 cm., on the dorsum of the left wrist (figure 9). It appeared verrucous in character, with papillomatous elements centrally. Pus could be expressed from many sites. There were small left epitrochlear and axillary lymph nodes.

A direct smear of purulent material expressed from the lesion was negative for *Blastomyces dermatitidis.* On culture a heavy growth of *S. schenckii* was obtained.

Iodide therapy, instituted on March 13, resulted in rapid involution of the lesion.

Comments: This represents an example of the fixed cutaneous type. The clinical appearance of the lesion suggested blastomycosis. There was rapid involution of the lesion with iodide therapy.

Case 10. A 70 year old retired farmer and lumber dealer was admitted to University Hospital on October 9, 1946. About four weeks earlier he had noticed an erythematous, pea-sized nodule in the sacral area. Within several days identical lesions developed on the right thigh and right temporal region. Despite intensive penicillin therapy a generalized eruption appeared about two weeks prior to admission. Some of the lesions became ulcerated and discharged a purulent material. Concomitantly, the patient became aware of swelling and tenderness of the hands and right great toe. He had lost 25 pounds in the preceding four months, but there were no other constitutional symptoms. The past medical history revealed that the patient had received roentgen therapy to a basal-cell carcinoma of the right cheek, with satis-

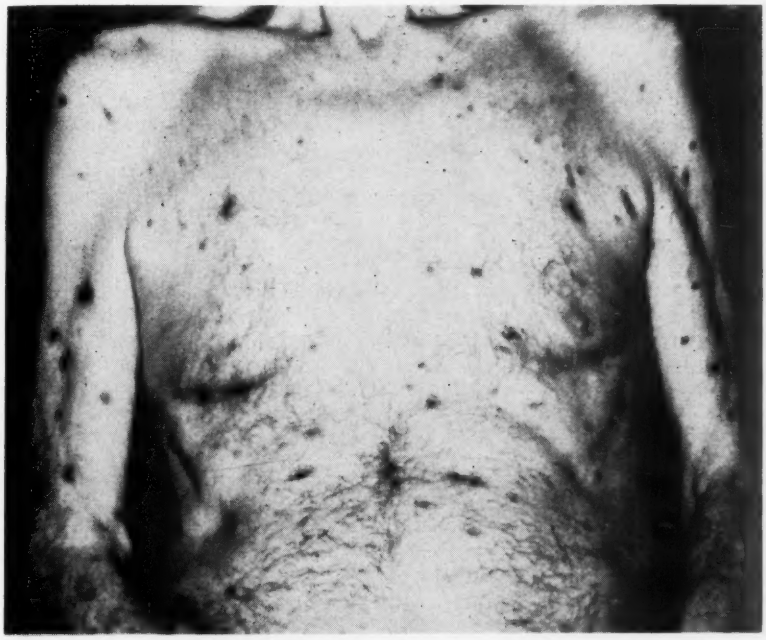

FIG. 10. *Case 10.* Hematogenous dissemination of sporotrichosis. Numerous erythematous papules and nodules were present over the entire body surface.

factory results, at the age of 62, and that he had had a transurethral resection because of benign prostatic hypertrophy four years later. He had had a chronic productive cough for many years and had been told that he had chronic bronchitis.

Physical examination revealed an elderly white male showing evidence of moderate loss of weight. Temperature was 99.2° F.; pulse, 90; respiratory rate, 22. Over the face, neck, trunk and extremities were "numerous, discrete, apparently indolent, match-head to small cherry-size polymorphous lesions. Many were firm, erythematous papules, while the central portion of others was soft, fluctuant and con-

tained purulent material. Some of the lesions had ruptured, with spontaneous evacuation of their contents, leaving central crater-like depressions, surrounded by a firm indurated ring. A few, probably the earliest, had practically healed" (figure 10).[16] There were slight swelling and tenderness of all fingers and some difficulty and discomfort in making a fist. The right great toe was swollen, tender and erythematous. There was evidence of moderate pulmonary emphysema. Cardiac examination was not abnormal. Blood pressure was 130/68 mm. of Hg. The spleen was palpable several centimeters below the left costal margin. The remainder of the physical examination was essentially normal.

Laboratory examination revealed a normal urine. The hemoglobin was 13.1 gm.; red blood cell count, 4.4 million per cubic millimeter; white blood cell count, 4,800 per cubic millimeter, with 72% polymorphonuclear cells, 12% lymphocytes, 13% monocytes and 3% eosinophils. Erythrocyte sedimentation rate was 38 mm. per hour. Serum Kahn reaction was negative. Repeated stool cultures were negative for organisms of the typhoid, paratyphoid and dysentery groups. A single blood culture produced no growth. The serum urate level was 2.6 mg. %. Tissue was obtained for microscopic examination from lesions on the back and forearm; the changes were interpreted as those of a chronic inflammatory process, with features of mixed tuberculous and pyogenic granulation tissue.

Material aspirated from a lesion on the left forearm was negative on direct examination for fungi and acid-fast bacilli. This material, on Sabouraud's medium, produced a prompt growth of *S. schenckii.*

X-ray examination of the chest revealed evidence of moderate bilateral pulmonary emphysema and a triangular shadow of increased density in the lower right hilar region with the apex directed toward the lateral thoracic wall. Atelectasis of the right middle lobe and pneumonitis of the right lower lobe were suspected. X-ray examination of the hands and feet revealed destructive lesions involving the proximal phalanx of the left fourth finger, the middle phalanx of the right fifth finger, the right fifth metacarpal bone and the proximal phalanx of the right great toe, with definite evidence of progression between October 11 and October 31, 1946 (figure 11).

Intensive iodide therapy resulted in prompt involution of the skin lesions, which did not recur. Additional roentgenograms on February 27, 1947, revealed no change in appearance of the chest but there was further progression of the destructive lesions noted previously in the hands and feet. This case was reported by Cawley [16] in 1949, when the preceding information was available.

The patient was seen on July 28, 1953, at which time he was re-admitted to the University of Michigan Hospital. Iodide therapy had been continued during the intervening six years, according to the patient. He stated that several months following his last visit, in February 1947, a draining sinus had developed at the tip of the left first toe. This healed spontaneously within three months, but was followed in a few months by a draining sinus over the left wrist which healed in about a year. In early 1949 a sinus tract appeared at the right elbow. This also healed spontaneously in a matter of months, but recurred approximately one year prior to his re-admission. There had been a copious drainage of yellow purulent material, plus occasional pieces of a solid material which "looked like cartilage" to the patient. During this 12-month period there had been tenderness and progressive weakness and limitation of motion of the right elbow. The patient had had occasional night sweats but no other systemic symptoms. He described a chronic cough productive of small amounts of mucoid sputum each morning.

Physical examination revealed a normal temperature. The right elbow was somewhat swollen and limited in both flexion and extension. There was a draining sinus on the lateral aspect of the lower right humerus. Other sinus tracts were present on the lateral aspect of the left wrist and the dorsal surface of the left first

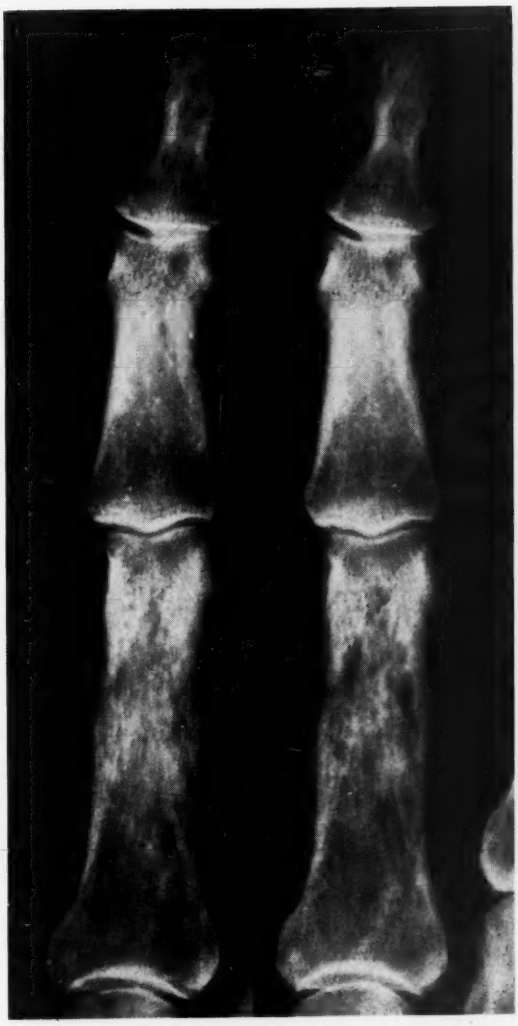

FIG. 11. *Case 10.* Progressive cystic rarefaction of the proximal phalanx of the left fourth finger occurring between October 11 and October 31, 1946.

toe. This toe appeared shorter than the right. There were numerous senile keratoses over the hands and face, an area of radiation dermatitis on the right side of the face and a 1 by 1.5 cm. crusted lesion on the right ear. The remainder of the physical examination was essentially normal.

Urinalysis revealed a slight trace of albumin and 15 to 20 white blood cells per high power field but was otherwise normal. Hemoglobin was 13.2 gm., and the white blood cell count was 5,200 per cubic millimeter, with 63% polymorphonuclear

cells, 13% lymphocytes, 23% monocytes and 1% eosinophils. A single culture of material from the draining sinus of the right lower humerus produced no growth on Sabouraud's medium.

X-ray examination of the chest revealed no change from previous examinations. There were widespread osteoporosis and destruction of the left carpal bones and the ends of the left radius and ulna. There were loss of joint space, irregularity of the articular margins, periarticular osteoporosis and soft tissue swelling about the right elbow joint (figure 12).

FIG. 12. *Case 10.* X-ray of the right elbow in July, 1953, showing juxta-articular osteoporosis, marked loss of joint space with irregularity of the articular cortex, and soft tissue swelling.

Biopsy of the right ear lesion revealed a cornifying squamous cell carcinoma. This, together with many of the senile keratoses on face and hands, was treated with electrodesiccation. The patient was discharged with instructions to continue iodide therapy.

In January, 1954, the patient reported by letter that there had been no change except for increasing disability of the upper extremities.

In May, 1955, the referring physician reported that the patient continued to have "multiple draining sinuses from bone, especially the humeri, in spite of large doses of iodides."

Comment: This represents an example of hematogenous dissemination of the organism with widespread involvement of the skin and articular tis-

sues. The skin lesions responded satisfactorily to iodide therapy, but articular involvement persisted and progressed despite continued therapy over a six-year period. This experience is in accord with that of Geraci and associates [24] who state that systemic sporotrichosis often fails to respond satisfactorily to iodides and therefore represents an indication for 2-hydroxystilbamidine therapy. In view of the subsequent course of this patient, it appears unlikely that the radiologic changes in the lungs were due to sporotrichosis.

Case 11. A 59 year old white male forge press operator and amateur gardener was first seen on August 4, 1955, with the chief complaint of arthritis. He had been in apparently good health until September, 1952, when the metacarpophalangeal joint of the left thumb became swollen, inflamed, stiff and painful. There was no preceding injury. About one month later the left elbow likewise became swollen, red, warm and painful. No skin lesions or nodules had been evident. There were no systemic symptoms, and the patient was able to continue work despite morning stiffness and pain on motion in these joints. In September, 1953, the patient began to experience aching discomfort in the right knee, which soon became swollen, erythematous and warm. A cyst appeared in the right popliteal area and persisted despite repeated aspirations. By the fall of 1954 he was forced to stop work and to use crutches because of pain in the right knee. In December, 1954, roentgen therapy was administered to the right knee, without benefit. In January, 1955, he was admitted to another hospital, where the diagnosis of rheumatoid and hypertrophic arthritis was made and an infected Baker's cyst of the right knee excised. Following this procedure, pain continued and a flexion contracture developed. The patient was readmitted to the same hospital in March, 1955, at which time a diagnosis of septic arthritis of the right knee was made. The posterior compartment was drained and a leg cast applied in an attempt to correct the contracture. Pain and disability persisted, however, and the patient was referred to University Hospital for further study. In the nine months prior to admission he had had frequent night sweats and a loss of 10 pounds in weight. He had been on a weight reduction diet because of mild diabetes mellitus, known since 1947. He had also had seasonal allergic rhinitis and bronchial asthma since 1937.

Physical examination at the time of admission revealed a well developed, moderately obese male who did not appear acutely ill. Positive findings were limited to the joints. The metacarpophalangeal joint of the left thumb was moderately swollen and tender. The left elbow was swollen, warm, tender and limited in motion. The right knee was swollen, slightly warm and tender over the medial aspect. There were severe pain and crepitus on motion. A scar was present in the right popliteal area, where there were also fullness, tenderness and a small sinus draining seropurulent material. A nodule 2 by 2 cm. in diameter was present on the medial aspect of the left knee, and there was atrophy of the musculature adjacent to the involved joints. The clinical impression was divided: some believed this represented atypical rheumatoid arthritis; other observers favored a probable specific infectious arthritis.

Urinalysis revealed 1 plus albuminuria and a trace of sugar on several examinations. The hemoglobin was 14.5 gm., with a hematocrit of 43 vol.%. The white blood cell count was 9,850 per cubic millimeter, with 56% polymorphonuclear cells, 27% lymphocytes, 5% monocytes and 12% eosinophils. The erythrocyte sedimentation rate was 36 mm. per hour, corrected. The serum Kahn reaction was negative. The serum urate level was 4.1 mg.%. Liver and renal function tests were within normal limits. A glucose tolerance test was diagnostic of diabetes mellitus. Blastomycin, coccidioidin and histoplasmin skin tests were negative; a 1:10,000 old tuberculin

skin test was positive. Punch biopsies of the synovium of the right knee were obtained on September 16 and October 6; on each occasion 37.5 mg. of hydrocortisone tertiary-butylacetate were injected intra-articularly, with symptomatic benefit. Material obtained at biopsy showed chronic productive synovitis with slight lymphocytic infiltration and abundant lime-salts beneath the synovial membrane (figure 13). There was no evidence of any specific chronic infectious granuloma, and the process was thought to be more compatible with a traumatic or neuropathic arthritis than with rheumatoid arthritis. It was not possible to obtain synovial fluid from the right knee,

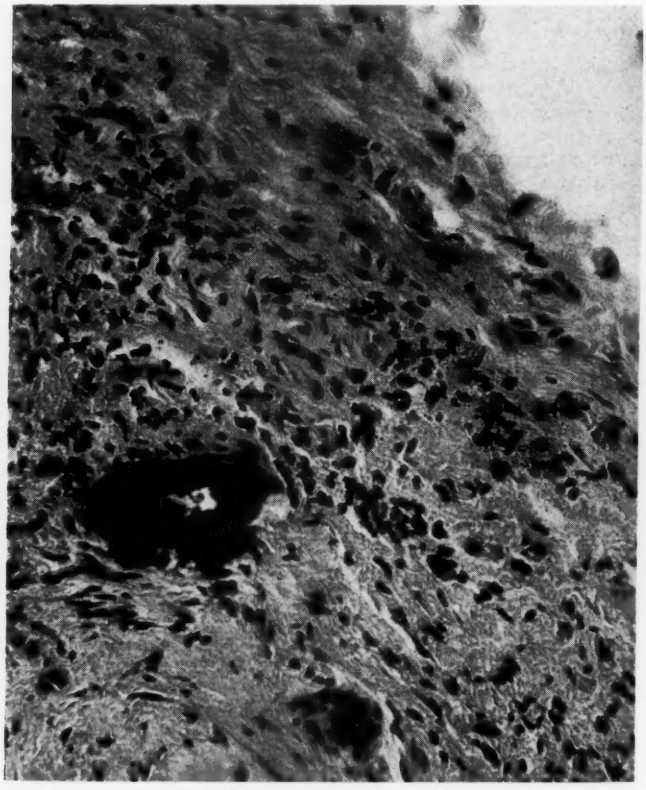

FIG. 13. *Case 11.* Punch biopsy of the synovium of the right knee, showing subsynovial inflammatory cell infiltration with scattered areas of lime-salt deposition.

but approximately 10 ml. of a thick serosanguineous fluid were aspirated from the left elbow on October 6. The total white blood cell count on this fluid was 18,150 per cubic millimeter, with 73% polymorphonuclear and 27% mononuclear cells. A specimen was sent to the Bacteriology Laboratory for culture for pyogens, acid-fast bacilli and fungi, and for guinea pig inoculation.

X-ray examination of the right knee showed juxta-articular osteoporosis, apparently complete destruction of articular cartilage, and lateral subluxation of the tibia and fibula on the femur (figure 14). There was complete destruction of

articular cartilage of the left elbow, with a pronounced degree of osteoporosis and marked irregularity of the opposing surfaces of the humerus and ulna (figure 15). Examination of the hands revealed subluxation of the proximal phalanx of the left first digit on the metacarpal with destruction of the adjacent bony surfaces (figure 16). There were no changes in the fingers or wrists suggestive of rheumatoid arthritis. Review of outside films revealed marked progression of destructive changes in the right knee between January 7 and March 28, 1955. The final radiologic impression was that of an infectious arthritis.

While in the hospital the patient was treated conservatively with bed-rest, salicylates and physical therapy. He improved symptomatically and was discharged, ambulatory on crutches, on October 14.

FIG. 14. *Case 11.* Right knee, showing destruction of articular cartilage, marked irregularity of the articular surfaces, lateral subluxation of the tibia and fibula on the femur, and periarticular osteoporosis.

Four days later it was reported that the culture of fluid from the left elbow had produced a pure growth of *S. schenckii;* cultures for pyogens were negative. The patient was readmitted on October 18 with the history that two days previously he had developed urticaria, wheezing, diaphoresis and fever. These symptoms had followed the administration of a barbiturate and, with the exception of the fever, were relieved by an antihistamine.

On physical examination the patient appeared acutely ill, with a temperature of 103° F. and respiratory rate of 44 per minute. The right knee was markedly swollen, hot and extremely tender to touch. The overlying skin appeared fiery red, with scattered pustular areas of necrosis. There was a profuse, seropurulent drainage from the sinus in the right popliteal area. A group of 2 cm. lymph nodes was present in the right inguinal region. The left elbow appeared more swollen and fluctuant than on the first admission.

Laboratory examination revealed a white blood cell count of 10,150 per cubic millimeter, with 53% segmented polymorphonuclear cells, 39% band forms, 6%

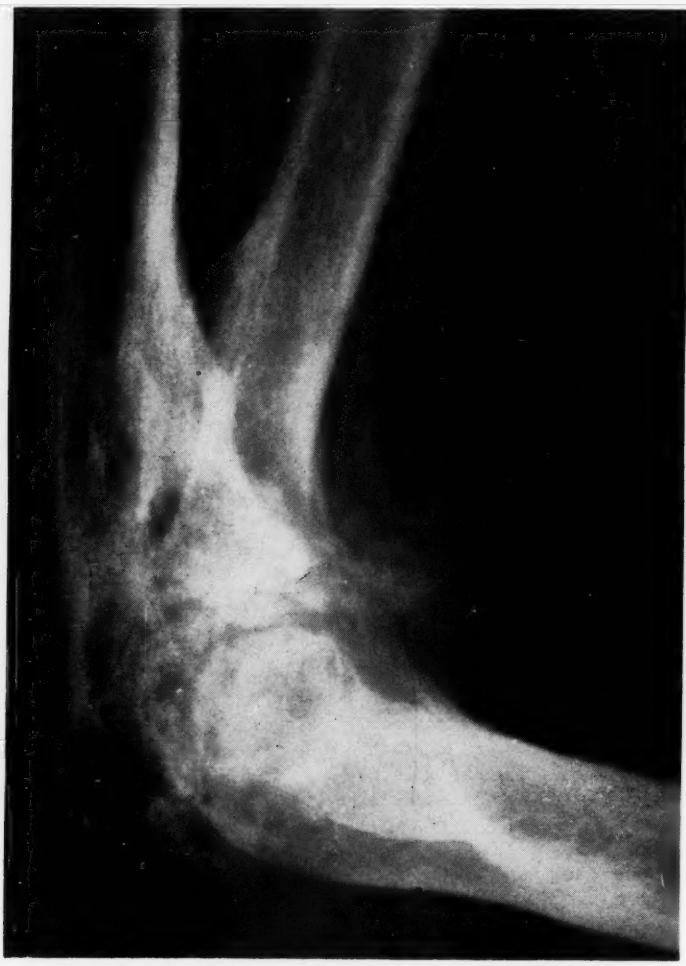

FIG. 15. *Case 11.* Left elbow, demonstrating virtual dissolution of the articular surfaces and advanced cystic osteoporosis.

lymphocytes and 2% eosinophils. There was 3 plus basophilic granulation of the neutrophils. Urinalysis revealed 3 plus albuminuria, 0 to 1 red blood cell and 3 to 5 white blood cells per high power field, and 15 to 20 granular and 1 to 3 hyaline casts per low power field. Coagulase-positive hemolytic *Staphylococcus aureus* (*Micrococcus pyogenes* var. *aureus*) was isolated from the throat, right popliteal sinus, right knee and the blood stream. Three consecutive blood cultures were positive; pour plates yielded 182 colonies per milliliter of blood. The organism was sensitive to erythromycin and Chloromycetin, and relatively resistant to penicillin.

The clinical diagnoses were sporotrichosis of the right knee, left elbow and metacarpophalangeal joint of the left thumb; superimposed pyarthrosis of the right

knee and left elbow, and staphylococcal septicemia. Upon admission the patient received large doses of penicillin and streptomycin, as well as potassium iodide. When the report of the sensitivity studies became available, erythromycin and Chloromycetin were added. On October 20 the right knee was incised and 500 ml. of a whitish, semisolid, caseous fluid were drained. The patient continued to have a fever of 103° to 104° F. and became delirious. On the evening of October 20 he developed urticaria and severe wheezing dyspnea. Epinephrine, aminophylline and Benadryl were administered, with only partial response. Intravenous hydrocortisone promptly controlled both the urticaria and the asthma. Fever persisted, however, and on October 23 the patient lapsed into coma and died quietly.

After death, cultures and guinea pig inoculation for acid-fast bacilli were reported negative. Material from a yeast phase culture of *S. schenckii* was injected intraperitoneally into a mouse on October 20. The mouse was sacrificed 30 days later and a culture mount from involved lymph nodes revealed the organism (figure 4). From the lymph node both the yeast and the mycelial phases of *S. schenckii* were readily recultured. The organism was again grown from material aspirated from the left elbow after death.

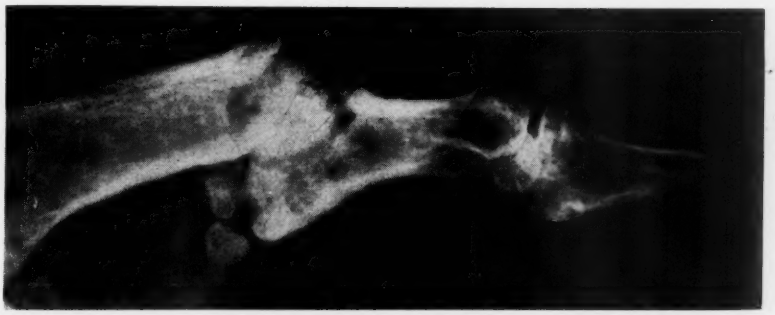

FIG. 16. *Case 11.* Left thumb, with striking destructive changes in articular cartilage and subjacent bone.

Postmortem examination was performed six hours after death. The positive gross findings included a surgical incision wound on each side of the right patella. Both wounds extended into the joint space, so that the femoral articular surface was readily visualized. The bone and adjacent musculature appeared necrotic. The joint space was filled with a pinkish, caseous material. A fluctuant nodule, 3 cm. in diameter, was present over the left olecranon process. This also contained a pinkish, caseous material. There was subluxation of the proximal phalanx of the left first digit. The left lung was bound down over the anterior and lateral portions by firm, fibrous adhesions. Except for emphysema, fine anthracotic stippling and congestion of the lower lobes, there was no abnormality of the lung. The heart weighed 450 gm.; the left ventricular wall measured 20 mm. in thickness, and the right ventricular wall, 5 mm. There were focal areas of myocardial fibrosis. There were no endocardial lesions and no thrombus in the left atrium. All branches of the coronary arteries showed advanced atherosclerosis, with marked diminution of their lumina. There was no recent or complete occlusion of any of the coronary vessels. The liver weighed 2670 gm.; the enlargement was predominantly of the right lobe. The spleen weighed 310 gm. but appeared normal. The pancreas weighed 130 gm. and showed marked fibrous and fatty atrophy. The adrenals weighed 9 and 11 gm., and there were marked obliteration of the corticomedullary demarcation and depletion of corti-

cal lipids. The kidneys each weighed approximately 280 gm. and appeared grossly normal.

Microscopic examination revealed minimal mucopurulent bronchitis and early lobular pneumonia. There were hyalinization of the basement membrane and hypertrophy of the muscularis mucosa of the bronchi. Advanced atherosclerosis with calcification of the coronary arteries was found. Slight chronic cholangitis was present. There were hyaline changes in the arterioles adjacent to glomeruli and retrogressive changes in the walls of glomerular capillaries. Subacute purulent and suppurative osteomyelitis of the right femur was found; numerous cocci and scattered periodic acid-Schiff-positive bodies were present. The organism could not be demonstrated in other tissues.

Comment: In this case there was no history of cutaneous involvement. Initially the diagnosis was confused with rheumatoid arthritis, inasmuch as articular manifestations dominated the clinical picture. Later, removal of an infected Baker's cyst and repeated aspirations of the posterior compartment of the right knee resulted in the additional diagnosis of pyogenic arthritis of that joint. Eventually a draining sinus formed in the right popliteal region. The joint disease progressed and systemic symptoms appeared. The diagnosis of sporotrichosis of the joints was established by culture of the organism from material from the left elbow. A fulminating staphylococcal septicemia developed and was considered the primary cause of death. The draining popliteal sinus was thought to be the source of the bacteremia, although the punch biopsies of the synovium and intra-articular injections of hydrocortisone could not be excluded as causative factors.

Case 12. A 26 year old female was employed as a mycologist by the University of Michigan Hospital. On April 5, 1956, while preparing culture mounts of *S. schenckii,* she accidently inoculated the tip of her right index finger. On April 19 a painless swelling was evident at the site of inoculation. This area became more and more erythematous and indurated, and on April 26 a small area of ulceration developed on the palmar aspect of the fingertip. Physical examination also revealed very small nodules along the lymphatic channels of the right forearm. No epitrochlear or axillary nodes were palpable. Cultures taken at this time produced an abundant growth of *S. schenckii* within four days. Potassium iodide was started on May 2 and resulted in virtually complete resolution of the lesion by May 23.

Comment: Laboratory infections are not uncommon.[25, 26, 27, 28] The mode of entry, clinical picture and subsequent course closely resemble the usual case of localized lymphangitic type.

Discussion

Sporotrichum schenckii may involve the articulations or bone by direct extension from cutaneous or subcutaneous lesions or via the blood stream. In the former instance the usual result is a periostitis with elevation of the periosteum and erosion of the cortex. Dissemination via the blood stream is the more common mode of infection. The organism may be seeded into the synovium, with resultant spread to adjacent cartilage and bone, or into the medullary region of bone directly. Lesions are frequently multiple, and

usually lytic and destructive in their radiologic appearance. Roentgenologically they are most often confused with tuberculosis, although they may also resemble metastatic neoplasm, destructive rheumatoid arthritis or other conditions. The organism may occasionally be introduced directly into the joint as the result of a penetrating wound.

Although there is general agreement that the incidence of most forms of specific infectious arthritis has decreased since the advent of effective chemotherapeutic and antibiotic agents, this may not be true in the case of infections due to the pathogenic fungi. The importance of mycotic infection in the etiology of bone and joint disease has been emphasized by the recent report of Toone and Kelly.[29] Of 25 cases of deep mycotic infection seen over a five-year period at the Medical College of Virginia, eight had involvement of articulations or bone. No cases of sporotrichosis were included. The possibility of mycotic infection must be considered in every case of chronic disease of bone or joints, but especially in those in which destructive changes are evident radiologically. Also, the failure to recover pyogens or acid-fast bacilli or to demonstrate a satisfactory clinical response to antibiotics or chemotherapy in cases suspected of being infectious in nature should alert one to the possibility of fungous infection. Accurate diagnosis rests upon a high index of suspicion plus the routine culture of appropriate material for fungi as well as for pyogens and *Mycobacterium tuberculosis*.

Summary

Twelve cases of infection with *Sporotrichum schenckii* are reviewed. In the majority of cases (83%) infection was limited to the skin and subcutaneous tissues. Diagnosis in each case was readily established by the use of routine cultural technics. Response to iodides was prompt and complete; stilbamidine and 2-hydroxystilbamidine have also been shown to be effective and are considered the treatment of choice in cases with disseminated disease.

Bone and joint involvement is not rare, occurring in 17% of the present series of cases. Whenever infectious arthritis is suspected, the possibility of sporotrichosis or other fungous infections should be considered and investigated.

Acknowledgment

The technical assistance of Miss Sylvia L. Laine is gratefully acknowledged.

Summario in Interlingua

Ben que sporotrichosis es usualmente restringite al pelle e al tessuto subcutanee, illo deberea esser classate con le mycoses profunde, proque dissemination extracutanee es possibile. Le infectiones cutanee es le plus frequentemente del typos localisate lymphangitic o cutanee fixe, sed multiple e extense lesiones pote resultar ab dissemination hematogene. Affection de membranas mucose, de structuras ocular, del visceres abdominal, de ossos, e de articulationes ha essite reportate. Casos demonstrate de affectiones pulmonar o gastrointestinal o del systema nervose central es extrememente rar.

Le agente etiologic es le fungo *Sporotrichum schenckii.* Ben que le organismo es rarmente observate in le examine directe de materiales del lesiones o de histosectiones, illo es facilemente isolate in culturas con agar a glucosa de Sabouraud. Su crescentia es biphasic. A temperaturas normal de interior, un rugate colonia de color nigre mat se disveloppa. Le examine microscopic de illo revela un crescentia mycelial con hyphas septate e racemos uvoide de microconidios ronde o oval que es attachate a lateral brancas conidiophoric. A un temperatura de 37 C, le phase saccharomycetic se disveloppa in le forma de un humide colonia blancastre que revela sub le microscopio structuras ronde o oval o del forma de cigarros. Iste structuras es frequentemente distinguite per le presentia de buttones.

Es presentate un revista de 12 casos de sporotrichosis observate al Hospital del Universitate Michigan. Cinque esseva exemplos classic del typo lymphangitic localisate. In omne istos, un primari lesion papular appareva al sito de inoculation intra un a quatro septimanas, sequite intra un mense per le apparition de un serie de nodulos subcutanee al longo del route de drainage lymphatic del lesion primari. Le administration oral de un solution saturate de ioduro de kalium resultava in quatro casos in un prompte e complete curation. In le quinte caso, le administration intravenose de stilbamidina produceva un equalmente favorabile resultato. Un caso additional de infection lymphangitic localisate resultava quando un assistente technic, qui manipulava culturas de *Sp. schenckii,* se inoculava accidentalmente. Lesiones lymphangitic localisate de sporotrichosis esseva confundite in un caso con pyodermia e in duo casos con actinomycosis cervicofacial a causa de lor sito e apparentia inusual. In omne iste casos, le correcte diagnose esseva promptemente establite per methodos de culturation. Un del duo ultimemente-mentionate patientes experientiava curation clinic post le administration intravenose de 2-hydroxystilbamidina. In un caso, un lesion cutanee fixe, que habeva essite presente durante plus que 18 menses, respondeva rapidemente a un therapia a iodo.

De interesse special esseva duo patientes con affectiones de structuras ossee e articular. In le un, le affection skeletic esseva associate con dissemination hematogene de lesiones cutanee. Therapia a iodo reduceva le lesiones cutanee de maniera satisfacente sed non sufficeva a arrestar le progresso del affection articular. In le secunde caso, nulle historia de lesiones cutanee poteva esser obtenite, e le correcte diagnose esseva establite durante un acute curso terminal complicate per septicemia staphylococcal. Il ha essite asserite que casos de sporotrichosis disseminate o extracutanee refusa a vices responder adequatemente a therapia a iodo e debe esser tractate con 2-hydroxystilbamidina. Es sublineate le importantia de obtener routinarimente culturas pro fungos si ben como pro pyogenos e bacillos acido-resistente in omne casos de suspicion de arthritis a infection specific.

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PULMONARY ATELECTASIS: PHYSICAL FACTORS*

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Introduction

Postnatal atelectasis refers to an airless state of the pulmonary parenchyma which occurs when tributaries serving it become obstructed and circulating blood absorbs the last vestiges of air. Ventilatory ebb and flow is a mechanical function conforming to physical laws. Measurements of volume rate of flow, linear velocity, pressures applied, the stress imposed on tissue, and the forces involved have disclosed a wide range of values, out of keeping with an older notion that breathing is relatively effortless. These define the physical nature of all ventilatory disorders, and the first part of this report deals with their relation to atelectasis. There follows a similar appraisal of the salient physical attributes of devices commonly employed for treatment. Clinical manifestations in patients prone to develop atelectasis are then compared with theoretic considerations. From such correlation one can derive certain principles concerned with the origin and treatment of atelectasis and in some instances specific therapeutic measures.

Patients suffering from severe chronic respiratory paralysis admitted to the Buffalo Respirator Center of the National Foundation for Infantile Paralysis provided an excellent opportunity to observe the natural history of the complication, which was supplemented by selected cases from an indexed series numbering nearly 400 subjects on whom ventilatory studies had been made for a great variety of breathing disorders. It is important to emphasize at the outset that atelectasis itself is but one facet of the broader problem of airflow mechanics, which is a dominant factor in nearly all chest diseases.

Physical Principles

The Breathing Bellows: Either of two methods is equally effective for distending the lungs: supra-ambient pressure delivered to the inside of the respiratory tract, called positive pressure breathing, or an equivalent subambient pressure applied to the outside, called negative pressure breathing. The first, a necessary recourse of primitive land vertebrates, has the important virtue of delivering the same static air pressure to all accessible lung segments. Negative pressure breathing is confined to mammalia, the pos-

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sessors of a diaphragm interposed between abdomen and thorax, and arched with convexity toward the latter. The separate thoracic space is then completely enclosed by a musculoskeletal wall capable of actively enlarging it for the purpose of inspiration, and strong enough in all its parts to create the necessary inspiratory pressures which can attain considerable magnitude—up to 22 to 28 cm. water, to overcome the static elastic tension of the lungs, and dynamic pressures of 40 mm. Hg (53 cm. of water) or more,[1] required to produce rapid inspiratory airflow. Passive expiration presents no problem as long as the lungs retain capacity for recoil. Active expiration requires participation of muscles enclosing the thoracico-abdominal space as a whole.

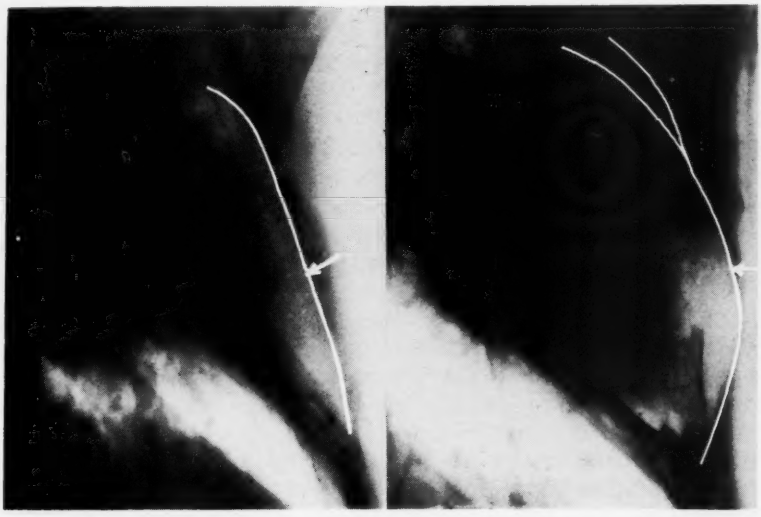

FIG. 1. Example of paradoxic ventilation. The line indicates the extent and position of the decostalized chest wall in a patient with thoracoplasty. The view on the left shows the resting position; that on the right shows protrusion of the wall and inflation of underlying lung when expiratory effort is made against a closed glottis. Position of the flaccid wall is determined by the difference between pleural and ambient pressure. Since pleural pressure fluctuates far more in response to dynamic conditions for flow than it does from the static conditions of lung tension, it follows that paradoxic movement of the chest wall and paradoxic ventilation are greater the more the effort employed in breathing.

In one way or another, atelectasis is caused by failure of the breathing bellows contingent on factors concerned with the statics of lung distention and dynamics of flow. Primarily it affects the inspiratory phase, limiting amplitude and speed of excursion, and reducing functional reserve volume. Pressure, flow and volume of passive expiration are indirectly impaired, since they are dependent upon the kinetic energy derived from preceding inspiratory muscular action. Expiratory defect is even more apparent when positive pressure is required in coughing, sneezing and loud phonation. But

failure of the bellows mechanism is not confined to overall weakness. Perhaps the most serious defect is failure of a *part* of the enclosing musculoskeletal wall. To create pressure in any confined space, the enclosing wall must be complete and competent to stand the stress. A large thoracotomy incision exemplifies a localized defect which renders the remaining wall impotent to create pressure. If a part of the chest wall is decostalized without penetrating the pleural space, the area is deformed by pressure. Under the high dynamic pleural pressure of cough, such a flaccid wall and the lung beneath it bulge outward with air derived from other parts of the lung, *paradoxic ventilation* (figure 1). Inspiratory pressures then return this twice-vitiated air to other pulmonary segments within. The functional effect ranges from impaired airflow to retrograde flow, depending upon the nature and extent of the defect and the magnitude of dynamic pleural pressure employed for breathing; but it can be accepted as a general principle that when a portion of the enclosing wall gives way, the underlying lung is hypoventilated and the situation invites cross ventilation with other lung segments, a major disaster when secretions follow the stream of flow. *Incomplete enclosure,* a term employed to designate failure of a part of the breathing bellows, is exemplified by instances of flaccid chest wall, paralyzed diaphragm, the flat mechanically ineffective diaphragm in emphysema, flaccid abdominal wall during positive pressure expiration, and by the action of the cuirass respirator.

The force of gravity and inertia of mass exert proportionately more effect when the bellows mechanism is weak than when it is normal. Neck muscles which could elevate the thoracic cage in a supine paralyzed patient may not be able to cope with the drag of thoracico-abdominal organs when erect. A comparable situation prevails when the strength of the diaphragm considerably exceeds that of the abdominal wall. The elastic force of the lungs is small when they are underinflated, so expiratory displacement of the diaphragm is accomplished by force of gravity in the supine patient and opposed by it when the patient is erect, unless abdominal support is provided. The situation is reversed when the force of gravity substitutes for inspiratory action of a completely paralyzed diaphragm. If abdominal strength is sufficient to cause expiratory displacement when the body is erect, such a patient may not be able to breathe unassisted when lying supine.

Rocking the body to produce ventilation employs not only the force of gravity but also to some extent the inertia of mass. It effects movement of the diaphragm, which causes ventilation, but the results are impaired by paradoxic movement of the chest structures. For this reason, tidal ventilation tends to be better on the rocking-bed when the paralyzed chest wall is stiff.[2]

Statics of Lung Distention: Over the range of lung volume corresponding approximately to that of the vital capacity, normal lung under static conditions reacts with counter pressure proportional to the volume of

air contained. For a given volume the pressure exerted is referred to as Lung Tension. The proportionality between change of tension and that of volume reflects one aspect of distensibility, which Meade [3] designated *pulmonary compliance.*

$$\text{Pulmonary Compliance} = \frac{\Delta \text{ Lung Volume in Liters}}{\Delta \text{ Lung Tension in cm. water}}.$$

Normal values in adults are 0.1 to 0.3 L. vol. per centimeter of pressure. They are determined from pressures in the esophagus or pleural space measured during the static interphase between breaths of known volume.

One factor which must affect the value for Compliance is the amount of lung subjected to distention. The range of Lung Tension in man and guinea pig is the same, but quite obviously more air is required to bring about a given tension in man. Similarly, twice as much air is needed for two lungs as for one. If some tributaries are completely blocked, Compliance is decreased in proportion to the amount of lung excluded. Disparity of resistance to flow between tributaries causes uneven distribution of air, which overventilates the more accessible segments. The more rapid the breathing, the greater the disparity. There being insufficient time for equilibration during the momentary interphase between breaths when static pressures can be measured, the values for Compliance tend to be lower during rapid breathing, since they reflect predominantly that of overventilated portions.

The fundamental aim of treatment is to convey air into obstructed lung segments without causing injury elsewhere. To define the limiting factors, one must distinguish between static and dynamic pressure. The latter must account additionally for resistance to flow, and also for the relatively small factor of tissue viscosity.

As a guide to treatment, it would be desirable to know the safe range of static pressure. At maximal inspiration, normal lung is under a tension of 22 to 28 cm. of water, and the excised organs unshielded by surrounding structures can be regularly ruptured at 50 cm. A safe limit should lie somewhere between, but unknown variables make clinical judgment difficult. Anatomic emphysema weakens lung structure and predisposes to spontaneous pneumothorax. Outside the body, 10 cm. water pressure has caused rupture.[4] In animals, focal noninflatable areas impose a greater strain of distention on neighboring parenchyma, the experimental equivalent of "perifocal emphysema" in man. Fleischner,[5] with good reason, ascribes the pathogenesis of anatomic emphysema to this mechanism. In practice, one cannot gauge the stress imposed on tissue from the static pressure applied without knowing how much is attributable to displacement of surrounding body structures which, in chronic respiratory paralysis, may be two to three times that required to distend the lungs themselves. Nor can the clinician scale the strain from over-all thoracic size if the proportion of lung contributing to such distention is unknown.

As for the obstructed airway, pressure in a rigid tube would propel a body within it like a piston. Human airways fortunately are distensible. They share the same elastic tension as the surrounding parenchyma. Static diameter therefore varies with lung volume, particularly in the delicate bronchioles. Static pressure, to dilate the airways, is confined within the range which spares the parenchyma from rupture. But airways obstructed by the apposition of walls or mucus must be penetrated by a hydraulic wedge of air. At the leading edge, where cohesion and surface tension offer maximal opposition, the distending force which pressure can directly exert is *zero,* since force is contingent on the area over which pressure is applied. The wedge advances rather through traction of the walls proximal to the apex. It is understandable that high pressure is required to force such an obstructed airway.[6-8] Anesthetists inform me that in thoracic surgery a collapsed but otherwise normal lobe may require as much as 60 mm. Hg pressure to initiate reinflation. The therapeutic dilemma in atelectasis rests precisely in the disparity between the pressure required to penetrate the airway and the distention which the parenchyma can safely tolerate. Solution is to be found in the use of dynamic pressures, exemplified by the observation of Day[9] that high pressure of brief duration could more readily relieve atelectasis in infants and with less risk to parenchyma elsewhere.

Dynamics of Flow: Air flows in response to pressure. Pressure declines downstream along the path of flow, the gradient. The more rapid the volume flow, or the greater the resistance, the more pressure is required and the steeper is the gradient. High insufflation pressure causes rapid flow to accessible segments and exposes obstructed tributaries to proportionately higher canalicular pressure. Most important of all, it establishes a high pressure difference between the inside and the outside of the airway, a powerful dilating force. As long as inspiratory flow is stopped prior to parenchymal dehiscence, high pressure should be not only safe but also desirable. These are merely the normal conditions for rapid inspiratory flow, pressures to a range of Müller's maneuver, 40 to 80 mm. Hg, peak airflow of 4 to 5 L. per second! Without normal provisions for terminating the effort, such pressures would be hazardous to apply artificially without accurate control of timing, as recommended by Day. Nevertheless, physical conditions for rapid flow are more effective than the static forces associated with volume for reinflating the airless lung.

Cough: Energy for breathing comes from muscular action which is deficient in debilitated, paralyzed, narcotized or comatose patients. They are obliged to carry on tidal breathing at small lung volume, and hence with smaller airways. This imposes higher resistance to flow, exaggerates that resulting from intraluminal obstructions, and renders airways more vulnerable to complete occlusion. The same changes cripple the cough mechanism, the very function needed to dispel them. It seems certain that, without some such means for clearing the major airways, pulmonary health and

possibly life itself could not be maintained indefinitely. It is not just a blast of air, but a breathing maneuver nicely designed to drive a jet through the bronchi and thoracic trachea at an astonishing linear velocity which expels secretions like projectiles from a gun. Intrathoracic airways are inherently checkvalves on expiration. Serious closure is normally averted by a number of factors, of which the most important is sufficient Lung Tension to maintain patency of the bronchioles and thereby minimize the pressure gradients associated with expiratory flow.[4] Cough is perhaps the single occasion in which expiratory checkvalve narrowing is physiologically solicited for a useful purpose. Even here it must not be excessive, lest secretions be trapped rather than expelled. Partial closure is made possible by the arrangement of cartilaginous rings and posterior membrane. This narrowing during periods of high expiratory flow has been observed for over a century, and various causes have been invoked, usually peristalsis.[10, 11] It can be seen on the fluoroscopic screen as a "wink" of the tracheal silhouette, far too rapid for the action of smooth muscle. If the trachea of excised and lifeless lungs is attached to a mechanical coughing device, the same phenomenon can be observed directly. It is independent of muscular, neural or humoral influences. Checkvalve closure occurs because the pressure driving air from the terminal spaces is applied as well to the walls of downstream airways in which canalicular pressure progressively declines along the path of flow. Preliminary glottic closure permits build-up of maximal intrathoracic pressure, which is necessarily followed in the expulsive phase by high transmural gradients for downstream points. As compression narrows the lumina, linear velocity is increased and volume flow decreased. To aid in understanding this aspect of body mechanics, observe that the wide-open nozzle of a garden hose gives a large volume of water with a short trajectory. Partial closure gives less volume but the stream emerges with great force, which carries it a maximal distance. Further tightening of the nozzle then cuts down both flow and velocity. Exactly the same principles apply to the stream of air sweeping through the respiratory tract, and with similar consequences. Earlier reports should be consulted for quantitative details regarding the cough mechanism.[1, 4, 12-14] One gains an appreciation of the enormous kinetic energy involved from the pressures exerted during cough in persons with intact muscles—100 mm. Hg or more. Such pressure applied over the cross-section area of the thoracico-abdominal space of a large man can represent an upward thrust against the lung bases in excess of 100 pounds! It is probably unwise to employ maximal, or Valsalva, pressures which in obstructive bronchopulmonary diseases can virtually arrest airflow [12] by causing complete checkvalve closure. Pressures on the order of 50 to 60 mm. Hg are probably optimal. Barach and Bickerman [15] employ pressures in similar range for therapeutic cough. Even at this pressure, natural cough requires strenuous physical endeavor, which imparts to the stream high kinetic energy linked to linear velocity—not necessarily to

volume flow. Ross [14] recorded pressure and volume flow during cough synchronized with cinefluorographic pictures of the tracheobronchial silhouette. Linear velocity in the trachea was computed in hundreds of miles per hour, and perhaps can attain momentarily the speed of sound! These considerations emphasize the woeful deficiency of cough in cases of respiratory weakness, a handicap made worse by atrophy of tracheobronchial cartilage converting these structures into limp tubes vulnerable to crushing under the slightest pressure. The aid of gravity, manual manipulation of the thorax, and a positive pressure phase within a tank respirator during expiration are convenient and useful measures, but functionally impotent in comparison to normal cough. The need for an effective substitute can hardly be questioned.

Physical Properties of Obstructing Agents: We cannot deal with this important subject in detail, but it should be noted that an obstructing body of fixed dimension would be less likely to arrest inspiratory airflow than would mucus or blood, which exhibit the properties of adhesiveness to give anchorage to the bronchial wall, and a yielding but elastic consistency which allows them to conform to airways of a wide range of diameter and shape. Clinically, atelectasis is most often associated with the presence of mucus or clotted blood.

Mechanical Aids to Breathing

To cope with problems of treatment, one must consider the essential properties of devices commonly employed to supplement or replace the natural function. Features of the principal types are listed below without going into details of operation or design.

Tank Respirator: One of mankind's most ancient devices, the lever, is so simple in operation and so dependable in performance that we are unlikely ever to dispense with it. Similar qualities commend the tank respirator among devices designed to assist ventilation through external application of negative pressure. A prime virtue is complete enclosure of all portions of the body subject to displacement.

The Cuirass Respirator: This device for producing negative pressure *partially* encloses portions of the body displaced during ventilation. The type which envelops the thorax alone tends to draw abdominal structures paradoxically into the chest during inspiration, and at the same time compresses the chest bilaterally where the edges impinge on the costal wall, particularly if it does not encircle the patient far enough posteriorly. Paradoxic movement is to some extent controlled by a padded rubber apron affixed to the lower edge, which tends to compress and immobilize the upper abdomen. If thoracico-abdominal structures move the wrong way, it is a functional advantage to fix them against any movement at all. One type of shell, when properly fitted, includes most of the anterior aspect of the abdomen almost as far as the symphysis pubis. More extensive enclosure

endows this type with greater capacity to ventilate the lungs. Stilts support the lower corners against the bed. A spreader bar partially resists the tendency to compress the sides of the body. With these exceptions, the subambient pressures acting on one part of the body to inflate the lungs must in turn be borne by other parts of the body wall upon which the edges of the device rest, namely, the upper thorax anteriorly, the lateral wall of thorax and abdomen, and the hypogastrium. These margins are compressed by the shell during inspiration when they should be free to expand. A hand placed beneath the patient will discern a tendency for the midportion of the trunk to be elevated from the bed by the partial vacuum created within the shell. Fortunately, this displacement is resisted by stiffness of the spine, and in the supine patient by force of gravity.

Viewed from the standpoint of ventilatory mechanics, the cuirass respirator, with an equivalent pressure, cannot give the tidal volume of a tank respirator, which provides complete enclosure. It causes such conspicuous distortion of the thorax that some degree of redistribution of air internally would be anticipated. We are not aware that it has been shown to cause atelectasis, but, confronted with ventilatory complications, there is cogent reason for the customary practice of resorting to a tank respirator or to positive pressure breathing.

The Rocking-Bed: As pointed out above, this device hurls the abdominal mass alternately toward and away from the lung bases, but the ventilating effect is limited by paradoxic movement of the chest.

Positive Pressure Breathing: Positive Pressure Breathing, applied by a face mask, a standard flanged mouthpiece, or a breathing tube of special design, has the advantage of delivering identical static pressures to all accessible parts, just as does the tank respirator. With either system there can be a disparity between tributary segments during actual flow, dependent upon the resistance offered by the respective airways. Technically it is easier to "push" air into the lungs than to "pull" it in. Simplicity of operation is reflected by the fact that with some methods either tidal volume, frequency, or both, can be controlled by the patient. It interferes with such functions of the upper respiratory tract as eating, but it enables the patient to ventilate in various body positions, including the standing posture, which would be difficult or impossible with any other method. Furthermore, it gives medical attendants free access to the body for other treatment.

It is relevant to observe that, in the anesthetized dog confined to one position, dependent parts of the lung become excluded from ventilation and Compliance is reduced.[16] Even distribution is restored by a few deep inhalations. Although the situation is different in man, he does, nevertheless, employ periodic deep inhalations, particularly when at rest. Rapid ample intake of air almost always precedes an effort to expel secretions. Control of positive pressure breathing by the patient gives recourse to this gratifying and salutary variation of tidal volume and speed.

Physiologists disagree about the effect upon the circulation. Findings here reported do not illuminate the problem. In these patients with chronic, relatively stable conditions, no adverse circulatory effects were observed. Had the need arisen, it would have been a simple matter to adjust some of the devices to * *positive-negative pressure breathing,* to prevent imposition of a mean supra-ambient intrathoracic pressure.

Demand Valves: Demand valves of standard design for resuscitation have the advantage of operating on either compressed air or oxygen, and can be adapted for aerosol treatment. Some types give rather limited volume flow, others have excessive pressure gradients, so that the addition of a narrow mouthpiece or an adapter for a tracheotomy tube may activate the valve from inspiration to expiration before adequate volume can be delivered. The patient applies mouth suction to start inspiration, and occludes the mouthpiece with a bite or the tongue to cycle to expiration. Within the capacity of the device to provide flow, the patient is in command of tidal range and frequency.

Cuirass Pumps: A similar end, but with automatic cycling, is achieved by adapting the pump for a cuirass respirator to give intermittent positive pressure. With reciprocating pumps, rubber checkvalves are incorporated in the tube conducting air to the mouth. The pump fills from the room and delivers air to the patient at approximately + 21 mm. Hg on the pumping stroke. Blower pumps are cycled by solenoid valves and do not require checkvalves in the breathing tube. The patient accepts only such pressure as is needed, dissipating the excess through partially open lips or nasopharynx. This dries the mucous membranes, but humidification is difficult to attain without complicated apparatus. Morch, Saxton and Gish [17] successfully treat even acute respiratory paralysis from poliomyelitis with positive pressure delivered through the uncuffed tracheotomy tube. Air is humidified by a "fog bottle."

Hand Bellows: Simplest of all is the fireplace bellows. Next to mouth-to-mouth breathing, said to have been employed by the Biblical prophet Elisha, it is probably the most ancient respiratory aid. Safe effective action is attested thousands of times daily in all parts of the world by the rhythmic pulsing of its modern counterpart, the rubber bag of an anesthesia machine. It is valved for filling, but there is no checkvalve at the tapered outlet. When hose is sealed around this, it creates an aerodynamic ramjet which prevents return flow almost as effectively as a valve. While the hand bellows finds its most important use as a breathing aid during transportation of patients, it is a convenient emergency device for general purposes, and it has been employed as an adjunct to other measures in the management of atelectasis. Its primary advantage is simplicity, which immediately makes it a familiar object, even to those untutored in the operation, maintenance and repair of mechanical contrivances.

* *Positive-negative pressure breathing* refers to devices which exert positive pressure to cause inspiratory flow and negative pressure for expiratory flow.

Therapeutic Cough: Despite the obvious need for and availability of mechanical devices adaptable for therapeutic cough, few investigators have explored their use. Outstanding among these have been Barach and his associates in the use of "exsufflation with negative pressure." [15] The foregoing expression designates the sudden application of negative pressure to the inside of the respiratory tract, as contrasted with positive pressure exsufflation involving pressure applied externally to the patient's body, which is entirely sealed within the pressurizing chamber except for head and neck. This latter method is far too cumbersome for general clinical use, but it has a signal advantage: it creates supra-ambient pressure within extrathoracic airways which keeps them open. Exsufflation with negative pressure tends

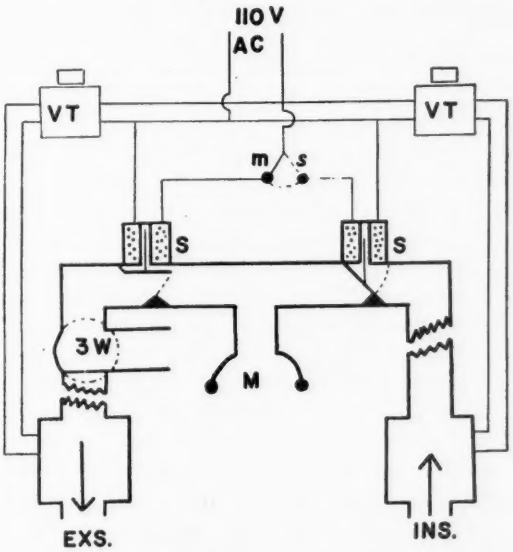

FIG. 2. Cough Caddy design. VT—Variable transformers, one controlling Insufflation Blower and one for Exsufflation Blower. S—Solenoid valves, one for insufflation channel, one for exsufflation channel. The solenoid valves are alternating, activated by a two-way microswitch. 3W—Three-way valve. M—Mask. EXS—Exsufflation blower. INS—Insufflation blower. The three-way valve and solenoids are set for patient exhalation at ambient pressure. The volume exhaled can be measured by connecting the side opening to a spirometer.

to collapse the upper respiratory tract. A patient can guard against this to some extent by splinting the floor of the mouth—if he is conscious and cooperative, and these muscles are not paralyzed. A rigid airway can be used in the unconscious patient. Profiting from the reports of Barach's group and their personal communications, we began this phase of the work in 1953, under the auspices of the Muscular Dystrophy Association, having in mind

certain specifications which have since been amplified. The device should give rapid inspiratory flow. Physical conditions should duplicate as closely as possible those of natural cough. This involves not only the sudden application of pressure but also a capacity to induce a high rate of expiratory flow. Conventional blowers, commercially available, can achieve these aims. The device must be quickly adaptable for giving simple breathing assistance to the paralyzed patient, and it must be able to do so for protracted periods. It must not introduce risk of communicating pathogenic organisms from external sources. The patient must not be obliged to rebreathe exhaled air in any significant amount. Noise should be eliminated as far as possible. The device should be designed for transport and operation by one person. The design in figure 2 embodies experimental attempts to attain these goals. One important aspect should be emphasized: unsealed blowers are not safe in the presence of high O_2 concentration or explosive gases.

A two-channel system is employed, united as near the mask as possible by a sterilizable T-fitting. Air is propelled by standard vacuum cleaner pumps, one for each channel. These utilize a two-stage blower powered by a universal motor, which give pressures as high at 120 mm. Hg and flow in great excess of respiratory need. Variable transformers adjust the pressure to useful levels but with ample flow for rapid equilibration of pressure between the blower and the mouth. Reduced load likewise reduces wear under sustained operation. Noise is reduced at the slower speeds. With simple soundproofing measures, and by spread of the stream of flow at the blower ports (where turbulence would otherwise be responsible for most of the noise), the device is made acceptably quiet during therapeutic cough. At the restrained pressures required simply to assist breathing, the machine is silent. A three-way valve can be set for exhalation at the ambient pressure and the measurement of Compliance Volume. Large tubing (1¼" inside diameter) promotes a rapid flow at low pressure and minimizes fluctuation in the exsufflation channel when its solenoid valve abruptly opens. These are standard fittings for automatic heating equipment and offer rather more resistance to flow than is desirable, but larger ones would mean added weight, and other types are often bulky or fail to seat tightly. The type employed operates reliably and quietly at pressures recommended for cough. Solenoid action opens the valve, pressure closes it. When they alternate, the open valve appears to close an instant before the other opens, since the interchange involves transfer of air within limits ascribable to Boyle's law. One model was mounted on a golf bag carrier, hence the designation Cough Caddy (figure 2).

There can be no fixed indications for therapeutic cough, but it seems reasonable to use the measure as frequently as physiologic cough would be employed in a patient who has the same need and who retains the faculty to cough at will. Brief, frequent periods of treatment are more effective in the long run, as will be shown. Sustained exsufflation pressures to milk

the smaller airways, alternated with repeated exsufflations at high lung volume, is a recommended approach. After stopping treatment one should observe the patient for a moment lest secretions be dislodged but not yet expelled from the larger airways. The patient soon becomes alert to the frequency and manner of application best adapted for his relief. The therapist must exercise patience and tact when introducing the procedure. The flow of air and the sudden changes in pressure are at first alarming. To oppose these actions is exhausting for the patient. Coördination with the device, letting the machine do the work, is necessarily less taxing than natural cough. It has been used 15 minutes every hour for 10 consecutive hours without unwarranted fatigue in a seriously ill patient. We have indicated that there is no way of gauging the safe limits for insufflation pressure, and that the high dynamic pressures employed by Day [9] would be unsafe unless time, flow and volume could be precisely controlled. We have not had the opportunity to explore these possibilities, and thus have employed static pressure up to 40 cm. water regardless of the patient's unassisted capacity to inhale. Insufflation is then followed by exsufflation at 50 to 60 mm. Hg pressure.

Clinical Observations

Compliance Volume: The foregoing considerations suggested a simple test by which the clinician can quickly detect ventilatory changes. It has proved helpful in following restoration of function, particularly in the presence of atelectasis. If air is insufflated by mouth or tracheotomy tube under a selected positive pressure (static) which insures appreciable distention but is within safe limits as far as pleural rupture is concerned, the volume which the patient can thereafter exhale should reflect, among other factors, the amount of lung inflated. It provides a single point on the volume/pressure curve for distention of the lung together with the surrounding structures. The first is designated *Pulmonary Compliance,* the second *Thoracic Compliance,* and both together comprise *Total Compliance.* Thoracic Compliance changes slowly—in response to stretching exercises, for example—and contributes to *gradual* change in Total Compliance. Rapid alteration in Total Compliance is ascribed to the pulmonary component, the amount of lung accessible to inflation, which can change with dramatic suddenness from development or release of obstruction. Since one pressure alone is employed, the result of the test for Total Compliance is referred to as *Compliance Volume.*

Change is the important feature, so base line measurement should be made early in treatment and repeated at frequent intervals, employing the same insufflation pressure, 21 mm. Hg in present cases. This compresses air about 3%, so the exhaled volume measured at ambient pressure is augmented in that proportion, a small error within the limits of accuracy required for clinical management. Any pump capable of delivering the necessary volume and pressure without danger to the patient can be employed

for the test. The Cough Caddy (figure 2) is conveniently adapted for the purpose. The three-way valve excludes the exsufflation blower and diverts exhaled air at ambient pressure to a volumetric device connected to the side opening. To elicit the static effect, pressure must be maintained until inflation is maximal. Most patients quickly become accustomed to positive pressure breathing and can assure unimpeded flow of air. They are encouraged to contribute their own effort in both phases of respiration. Several tests are made, and if comparable values are obtained the largest is selected as the Compliance Volume. Since the settings of the Cough Caddy are similar for intermittent positive pressure breathing, even a totally par-

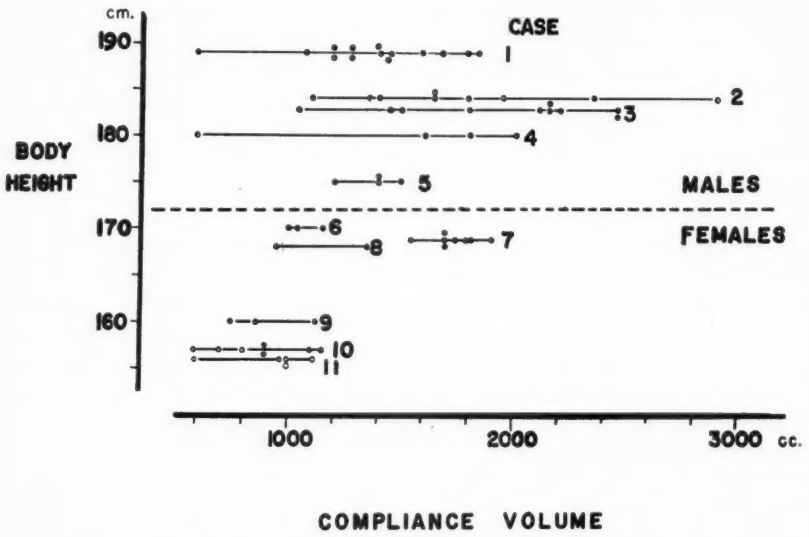

FIG. 3. Compliance Volume, height and sex. The term refers to the volume of air which could be exhaled by patients with breathing paralysis after inspiratory assistance of 21 mm. Hg pressure, maintained until inflation reached static equilibrium. Case numbers shown on right.

alyzed patient can be removed from a tank respirator or other aid and carried on ventilation by the Cough Caddy for indefinite periods. Minor modifications of the procedure permit correlation with body position, paradoxic movement, and x-ray or fluoroscopic changes. Particularly important, the results of therapeutic cough in the treatment of atelectasis can be evaluated without interrupting ventilatory assistance to the patient.

Figure 3 illustrates the relation to sex and body height. In general, range Compliance Volume approximates one third of the anticipated normal vital capacity for young adults of either sex. Weakness and immobility cause stiffness of the breathing bellows as they do in a paralyzed extremity,

and similarly aggravate the handicap, limiting alike the response to breathing aids and action of intact muscle remnants which might otherwise be trained and strengthened. Muscle training assisted by thoracic stretching with positive pressure and manual manipulation brings gradual symptomatic improvement and corresponding changes in the usual ventilatory tests. If paralysis was so extreme that restoration even of slight muscle function was not to be expected, the tests dependent upon the patient's effort remained unaltered, but better response to artificial aids contributed comfort and

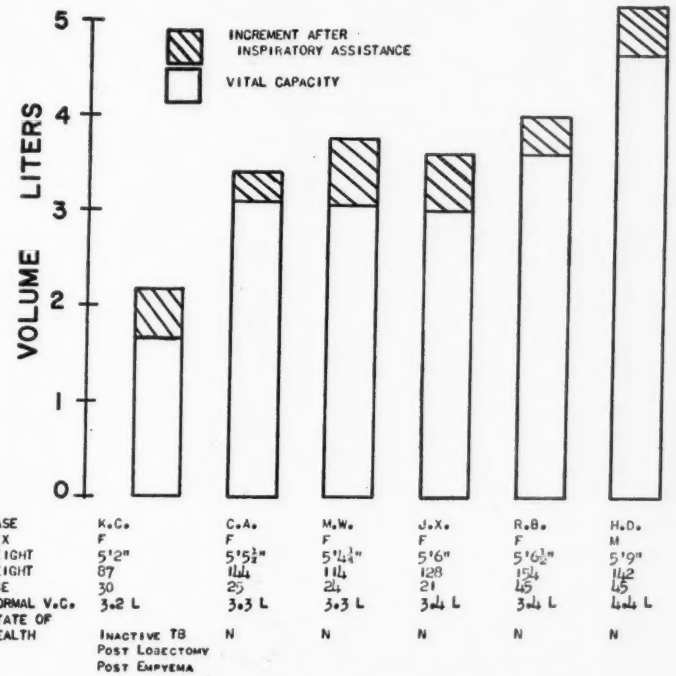
INCREMENT AFTER INSPIRATORY ASSISTANCE
VITAL CAPACITY
VOLUME LITERS
5
4
3
2
1
0
CASE K.C. C.A. M.W. J.X. R.B. H.D.
SEX F F F F F M
HEIGHT 5'2" 5'5½" 5'4¾" 5'6" 5'6½" 5'9"
WEIGHT 87 114 114 128 154 142
AGE 30 25 24 21 45 45
NORMAL V.C. 3.2 L 3.3 L 3.3 L 3.4 L 3.4 L 4.4 L
STATE OF HEALTH INACTIVE TB POST LOBECTOMY POST EMPYEMA N N N N N

FIG. 4. Vital capacity compared with Compliance Volume in healthy (nonparalyzed) subjects (see text). A patient with ventilatory handicap from tuberculosis and extensive thoracic surgery is compared with five normal persons.

safety. Compliance Volume paralleled the sum total of these changes, and it could attain several times the initial value in patients retaining sufficient muscle ultimately to contribute a substantial measure of their own effort for breathing. There were few such patients in this seriously handicapped group, but the same insufflation pressure applied to healthy subjects (figure 4) increased the vital capacity in the order of 10 to 20%. Approximately 3% of this was due to gas compression, but in some instances the remaining increment was appreciable, and it was observed to be highest in persons

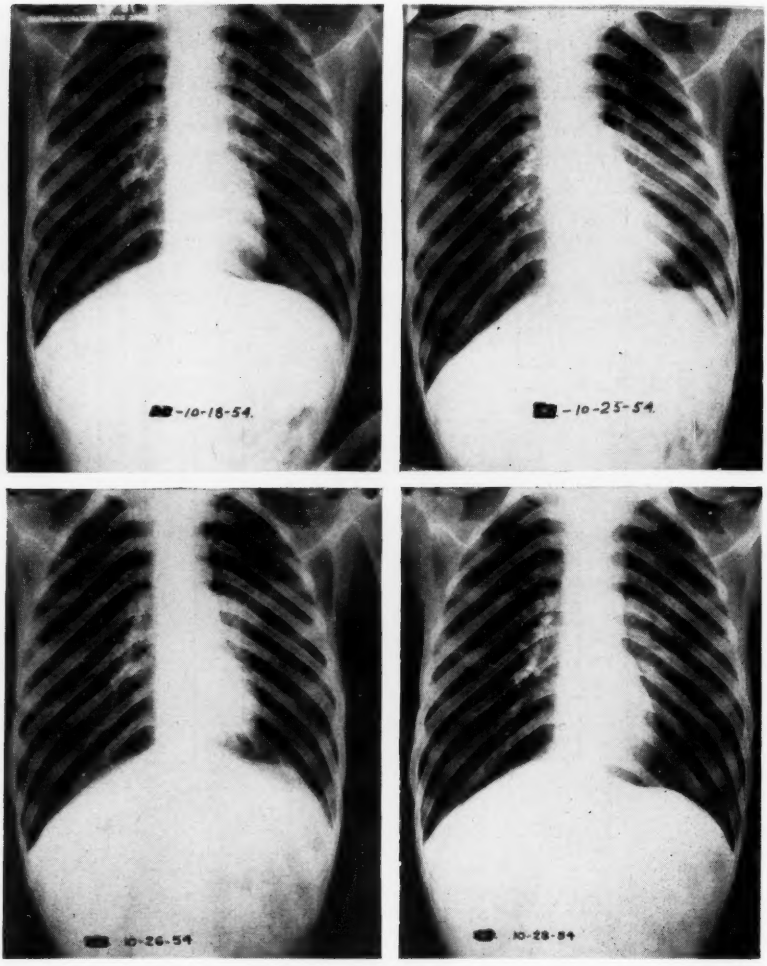

FIG. 5A.

lacking good coördination between diaphragm and chest wall during unassisted maximal inspiration.

Atelectasis—threatening, partial or complete—could suddenly reduce Compliance Volume to as little as 0.6 L., although the change was usually more moderate, in proportion to patient's height and previous range. Details are presented in the case reports.

The dynamic pressures within a tank respirator during active breathing do not reflect Compliance alone, unless pressures would be held at a fixed level long enough for a breath to terminate under conditions of static equi-

librium. For a given range of pressure fluctuation, tidal volume is necessarily less than Compliance Volume, the difference being due to airway resistance. A study of tidal volume and tank pressures in six patients did disclose the fact that a positive expiratory pressure as high as + 7 cm. water contributed no more than 100 c.c. to the volume exhaled, a manifestation of the small lung volume at which tidal breathing was conducted.

Case Reports

Case 1. This male patient, age 25, came to us with virtually total respiratory paralysis of one year's duration, a result of poliomyelitis. Unassisted tidal volume was 0.05 L., limited to seven breaths. Urolithiasis with concomitant infection was a perpetual problem which interfered with respiratory management. In two years Compliance Volume rose from 0.6 to 2.0 L. Figure 5 indicates salient changes during an acute respiratory infection. Clinical signs of coryza led to retesting Compliance Volume. It was not alarmingly depressed, but on October 18, 1954, it was still lowered, so a roentgenogram was taken under positive pressure inflation at 21 mm. Hg. Compared with previous films, there was a scarcely detectable shift of the mediastinum to the left, slight elevation of the leaf of the diaphragm and questionable haziness of the left lung field, changes which would be imperceptible unless exposure were made under inspiratory conditions. Antibiotics, inhalation therapy with bronchodilators,

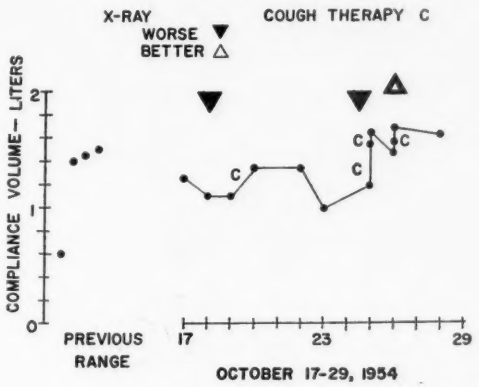

Fig. 5B.

and a detergent (Alevaire), together with humidification and head-down position, had not altered the clinical condition by the following day. By October 20 cough therapy had brought measurable improvement, which was maintained for a time, but a precipitous drop in Compliance Volume was detected on October 23, and a roentgenogram taken on October 25 confirmed the presence of more extensive atelectasis. Energetic cough therapy gave an abrupt increase in Compliance Volume. Concurrently, symptoms improved. Regression during the night was again controlled with cough therapy and confirmed by x-ray on October 26. Thereafter the respiratory complication was entirely dispelled, as seen by an x-ray taken on October 28, 1954, and Compliance Volume was maintained at higher levels than the previous range.

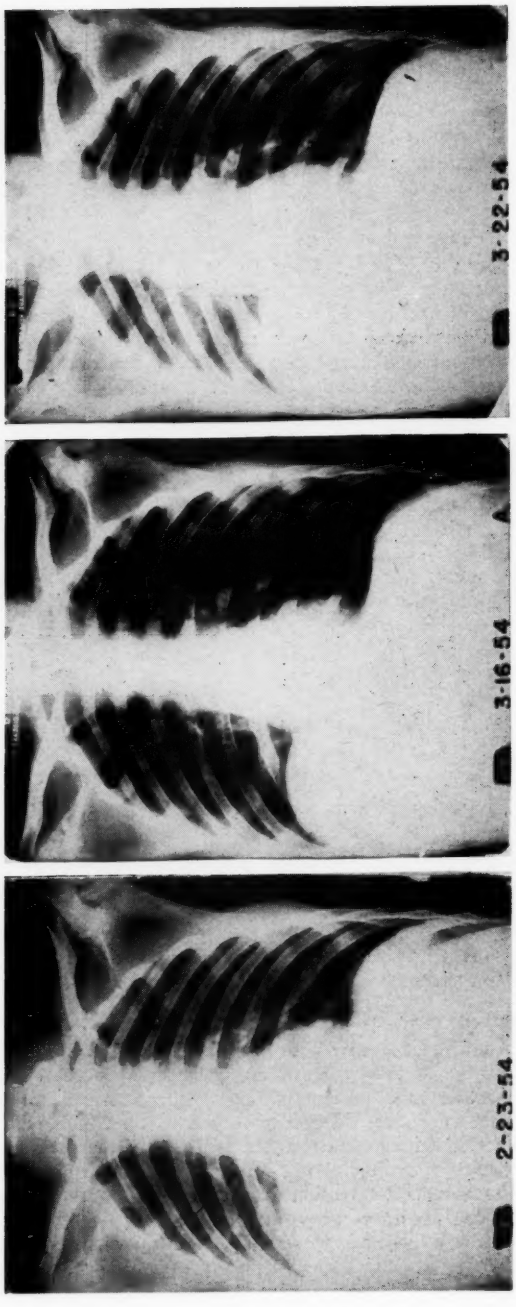

FIG. 6A.

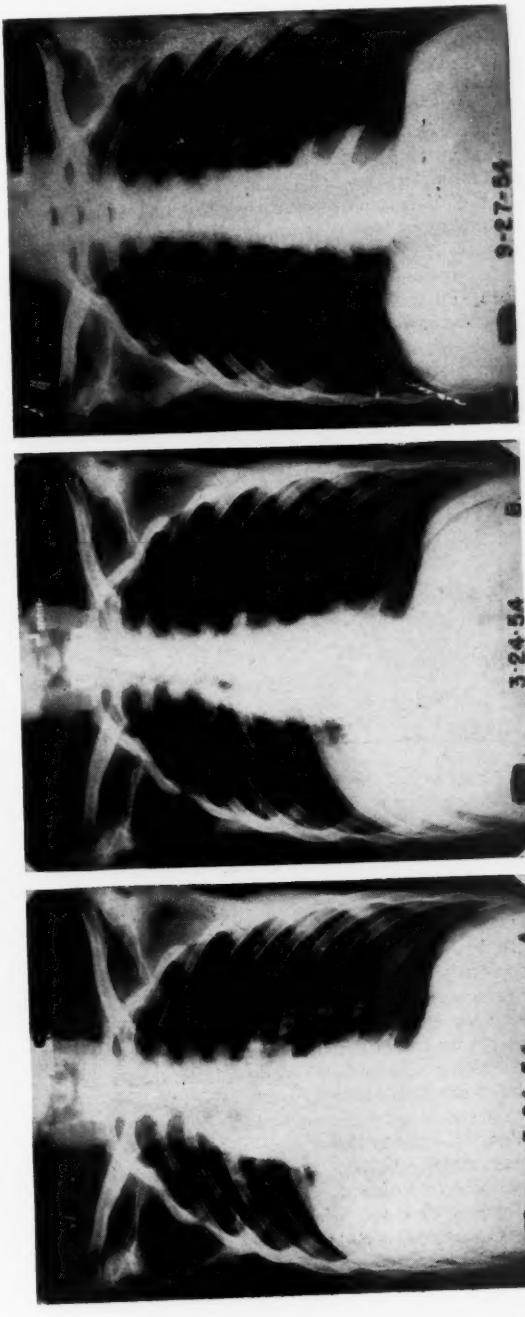

FIG. 6B.

Respiratory embarrassment results primarily from airway obstruction, not from the atelectatic state, and does so before absorption of air is roentgenographically demonstrable. In this preliminary and very labile *stage of inflation without ventilation,* conditions are ideal for effective cough therapy. Need for treatment was promptly recognized by determining the Compliance Volume. The immediate improvement in Compliance Volume and symptoms following therapeutic cough leaves no doubt of its efficacy. Used more frequently, it might well have prevented the adverse developments on October 26, 1954. During the bronchorrheic stage of bronchitis, the threat of mucus obstruction is constant. Brief periods of cough 10 or 12 times a day would more nearly approximate the frequency of physiologic cough under like circumstances. Prophylactic cough therapy and regular thoracic stretching have brought a distinct decline in the incidence of fullblown atelectasis among our paralytic patients. In addition to illustrating the use of positive pressure devices for this purpose, case 1 illustrates the salutary effect of glossopharyngeal breathing. During a two-year period, unassisted tidal breathing increased to only 0.2 L., and could not meet the functional demand for O_2 even for brief periods. With breathing

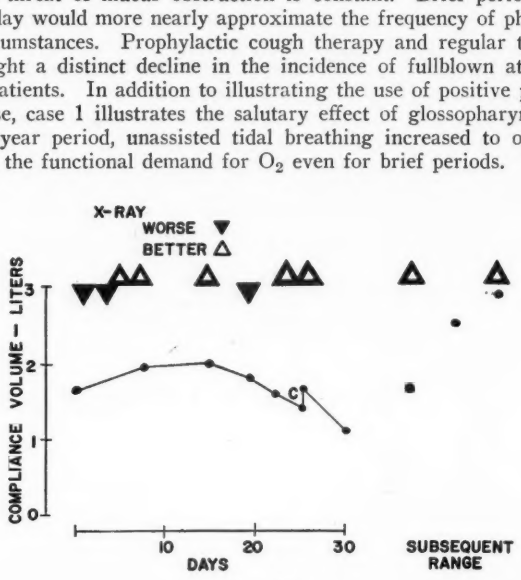

FIG. 6C.

aids, the tidal volume ranged from 0.4 to 0.5 L., but with glossopharyngeal breathing it was about 0.7 L., and the volume exhalable after a maximal effort by this means was 2.4 L.

Case 2. This male patient, age 26, developed poliomyelitis in 1952. Respiratory paralysis was severe but not total. Nevertheless, recurrent atelectasis necessitated repeated bronchoscopic aspirations and the establishment of a tracheotomy for daily suction. When he came to us a year after onset, the right lower lobe was persistently atelectatic, a condition more difficult to relieve because of concurrent suppuration and fibrosis. In this patient we tested the regular use of positive pressure to hyperinflate the lungs and to relieve thoracic stiffness by manual manipulation. Roentgenograms of February 23 and March 16, 1954, in figure 6, indicate the volumetric improvement. An atelectatic lobe remained almost concealed behind the elevated right diaphragmatic leaf, which was weaker than that of the opposite side. In the succeeding 30-day period there were alternating, usually fleeting, exacerbations of atelectasis and reëxpansion, indicated by the symbols in figure 6. In our initial experience with Compliance Volume the measurements were too infrequent to reflect these changes with fidelity. Therapeutic cough (C in the diagram) was shown to produce immediate expectoration of mucus and a parallel increase in Compliance Volume, but for comparable pres-

sures, catheter suction through the tracheotomy tube had a similar effect. In view of the purulence of secretions welling from the airless offending lobe, catheter suction to the specific area was deemed the treatment of choice. A given pressure (10 mm. Hg) forces mucus more readily through a large rather than a small opening. Thin-walled plastic catheters of 4 mm. outside diameter have internal dimensions exceeding 3 mm. Coiled in Zephiran, they retain a curve. A flag of adhesive at the proximal end during use indicates the direction of the tip, which is first passed through the major ventilating airways to be sure they are clear, then into the diseased lobe, feeling for successive tributaries step by step. We have checked this procedure aided by small amounts of lipiodol under fluoroscopic control, and must admit that it may be impossible to enter segmental bronchi by any means short of endoscopic vision, possibly because of angulation and displacements, but bronchoscopy is not permissible for day-to-day treatment over long periods.

An additional physical principle deserves comment. Mucus is forced into the catheter by the pressure gradient at the orifice on which the mucus impinges. Additional holes simply reduce the pressure gradient for each one. A catheter tip, cut off square or on a slight bias, should be most effective, and certainly there is no reason to suppose that holes along the side would improve it. Suction must be applied gently.

Case 2 was concurrently placed on positive pressure breathing by means of a

TABLE 1

Body Position	Abdominal Support	Head Stabilization	c.c. Tidal Volume
Supine	None	By gravity	400
Supine	Present	By gravity	300
Sitting	None	None	200*
Sitting	Present	None	300
Sitting	None	By brace	400
Sitting	Present	By brace	450

* Could not be maintained unless assisted by glossopharyngeal breathing.

When supine, the force of gravity helped neck muscles to elevate the thorax, and aided abdominal muscle. Sitting position helped the diaphragm but crippled the abdominal muscles. Tidal volume could be more than doubled by proper balance of these forces.

demand valve cycled by mouth pressure. Periods of treatment were increased gradually until they totaled several hours a day, and the patient was encouraged to hyperinflate the lungs as frequently as comfort would permit. Aerosol medication similar to that in case 1 was employed. In the succeeding six months the atelectasis was completely dispelled, and inflation has been maintained by persistent but less frequent application of the same measures. In figure 6 the improvement resulting from cough therapy is indicated by films of March 22 and March 24, 1954, A and B. The film of September 27, 1954, shows the ultimate therapeutic result from a roentgenographic standpoint. During this period Compliance Volume rose to 3 L. Volume exhalable after maximal glossopharyngeal inspiration reached 3.5 L.

This patient demonstrates in certain respects the added handicap resulting from disparity of strength between one and another portion of the breathing bellows. Persistent atelectasis of lung overlying the weaker diaphragmatic leaf has been mentioned. Body posture brought out interesting changes in tidal volume. It rose from 0.2 L. (which could not be long maintained) to the range indicated in table 1.

Case 3. This male, age 18, came to us in the post-acute stage of poliomyelitis. Over-all respiratory handicap was less formidable than that for most of his fellow patients. Within two years vital capacity increased from 0.6 L. to 1.2 L., and the maximal breathing capacity reached 74 L. per minute! Imbalance of strength be-

tween parts of the breathing bellows was brought out by altering body position. Supine, with or without an abdominal binder, the vital capacity in one series of tests was 1.2 L. Expiratory reserve was zero, the tidal expiratory position in these patients being close to the ultimate. In the sitting position, vital capacity dropped to 0.8 L. but was restored to 1.0 L. by abdominal support. This increment was contributed by expiratory reserve. The relatively competent thoracic cage, in conjunction with the diaphragm when it was assisted by gravity, could maintain a larger lung volume, but the relatively weaker belly wall could not deflate the lungs when opposed by gravity in the sitting position. These changes may seem small, but we are using volume as a scale of muscular power. Breathing which requires a wider swing of dynamic intrathoracic pressure enormously exaggerates ventilatory failure caused by weakness of a part of the enclosing bellows. One such maneuver is cough. Tidal ventilation in the presence of airway obstruction is another.

Thus in case 3, despite a generally favorable functional condition, the onset of an acute respiratory infection was followed by a pronounced decline in Compliance Volume (figure 7), accompanied by acute dyspnea. The roentgenogram of the chest showed no definite abnormality in the lung fields, but immobility of the left hemithorax

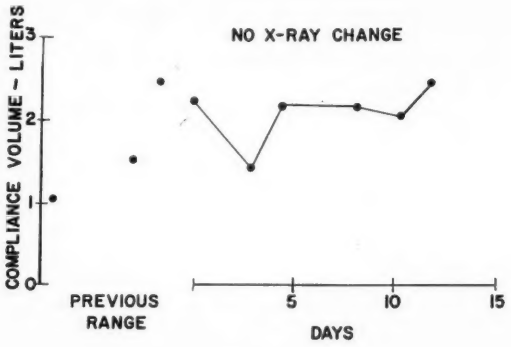

FIG. 7.

directed suspicion to that side. Energetic cough therapy brought forth abundant viscid mucus and symptoms immediately abated. The same treatment, continued through the period of bronchorrhea, maintained free passage of air and an inflated parenchyma. After returning home this patient has had similar episodes, with the same response to treatment. Case 3 emphasizes that cough therapy can be highly effective when used early, and that the signal indication is not atelectasis but the presence of secretions.

Case 4. This male patient, age 25, had chronic partial respiratory paralysis. No respiratory complications were encountered. The single low value for Compliance Volume, 0.6 L. (figure 3), is probably artifact. When the test is performed, duplication must be sought with safeguards against leakage and an eye for judging the patient's coöperation.

Case 5. This male patient, age 32, exhibited total respiratory paralysis but, oddly enough, retained sufficient strength in the legs and back to stand with the assistance of braces and to walk a few steps. Positive pressure breathing, used extensively, together with other measures to assure adequate pulmonary inflation, undoubtedly contributed to freedom from respiratory complications. Airway obstruction is by no means related to the over-all severity of the paralysis. Rather, there

is a strong suggestion that atelectasis is more prone to occur when a *part* of the bellows mechanism is disproportionately weak.

Case 6. This female, age 19, required a tracheotomy during the acute stage of poliomyelitis. Respiratory paralysis was severe but not total. Unassisted vital capacity in the succeeding two years rose from 0.3 to 0.5 L. A handicap of this degree permitted fair latitude in sedentary activities but strength was not sufficient to avert atelectasis in the presence of acute respiratory infection, which contributed to a fatal outcome after the patient returned home.

Figure 8 illustrates the inadequacy of cough when the capacity for active expiration is limited or absent. Following unassisted inspiration, the weakness of the expiratory effort was revealed by poor acceleration, low peak flow and no evidence of point of closure. Glossopharyngeal inspiration of 1.5 L. permitted a more rapid expiration but not one comparable with cough.

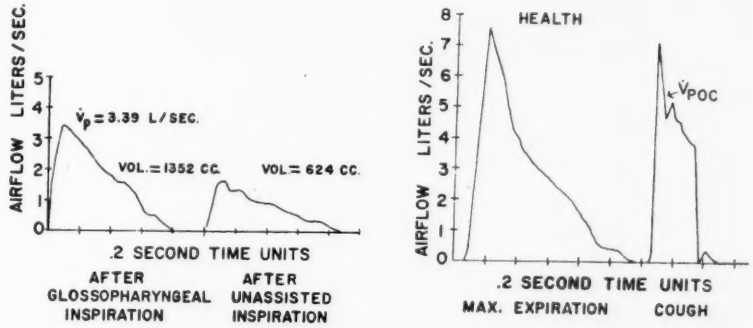

FIG. 8. Inability to cough in severe partial respiratory paralysis. Expiratory patterns at the left illustrate the efforts of case 6. Those of normal woman (G. S.) of similar age and stature are shown on the right. Case 6 achieved fairly good rates of expiratory flow following inspiration by glossopharyngeal breathing, but could not reproduce the pattern of cough. Acceleration was slow, and the pattern of deceleration was that of a moderately active expiration, both reflecting the recoil of lung and surrounding structures, with little muscular participation.

By comparison, G. S. showed greater flow and volume in a maximal expiration, the airflow equivalent of a vital capacity spirogram. Cough is distinguished by extremely rapid acceleration, made possible by mounting pressure behind a closed glottis. Peak flow is characteristically brief and terminates by a sudden decline associated with partial collapse of the cartilaginous airways at Point of Closure (POC). As the airways rebound (bronchial rebound), the air with which they fill is derived from the outflow stream and creates a notch in the pattern. Leakage flow continues at a level determined in part by bronchiolar caliber which, in turn, reflects Lung Tension. Fluoroscopic evaluation of tracheobronchial diameter indicates a linear velocity in the trachea at 300 to 400 miles an hour.

Case 7. This female, age 35, came to us with a more compliant thorax, which probably accounted for the relatively slight subsequent improvement. Vital capacity increased from 0.5 to 1.1 L. but depended upon body position. One leaf of the diaphragm retained considerable strength. Characteristically, there was a history of obstruction to the lower lobe overlying the opposite flaccid leaf in the post-acute stage. The belly wall was too weak to displace the active diaphragmatic leaf adequately when opposed by the force of gravity. Thus, in one series of tests the vital capacity of 1.1 L. when supine became 0.5 L. when sitting, but an abdominal binder restored it to 0.8 L. Early in the period of rehabilitation this patient was aphonic in the erect or semirecumbent posture. Vowel phonation requires a pressure of about 6 cm. water, which will give one a scale for appraising the severe handicap.

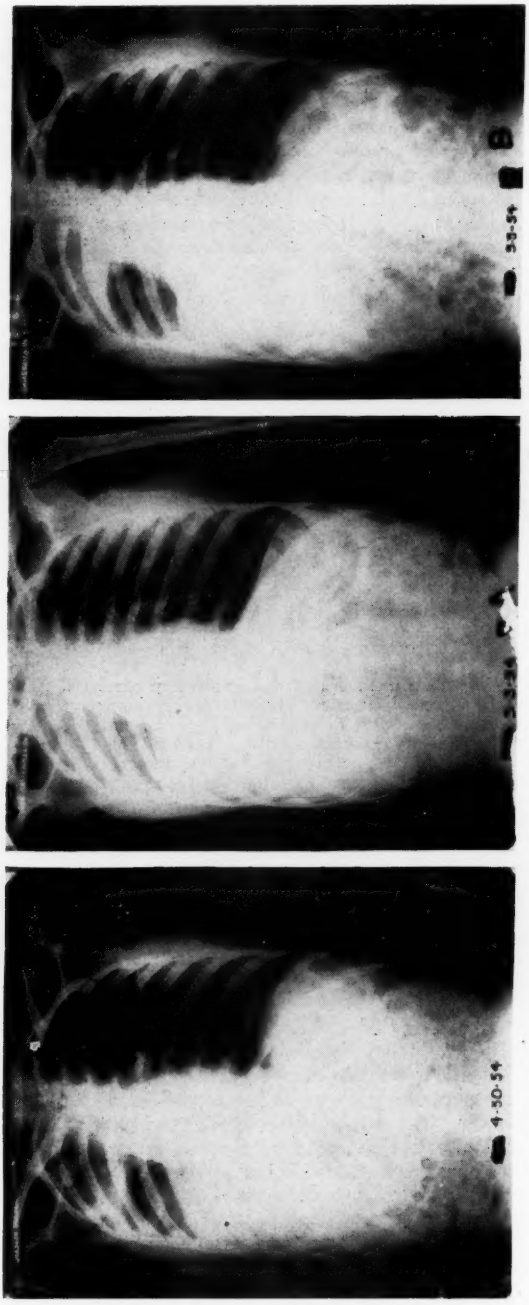

FIG. 9A.

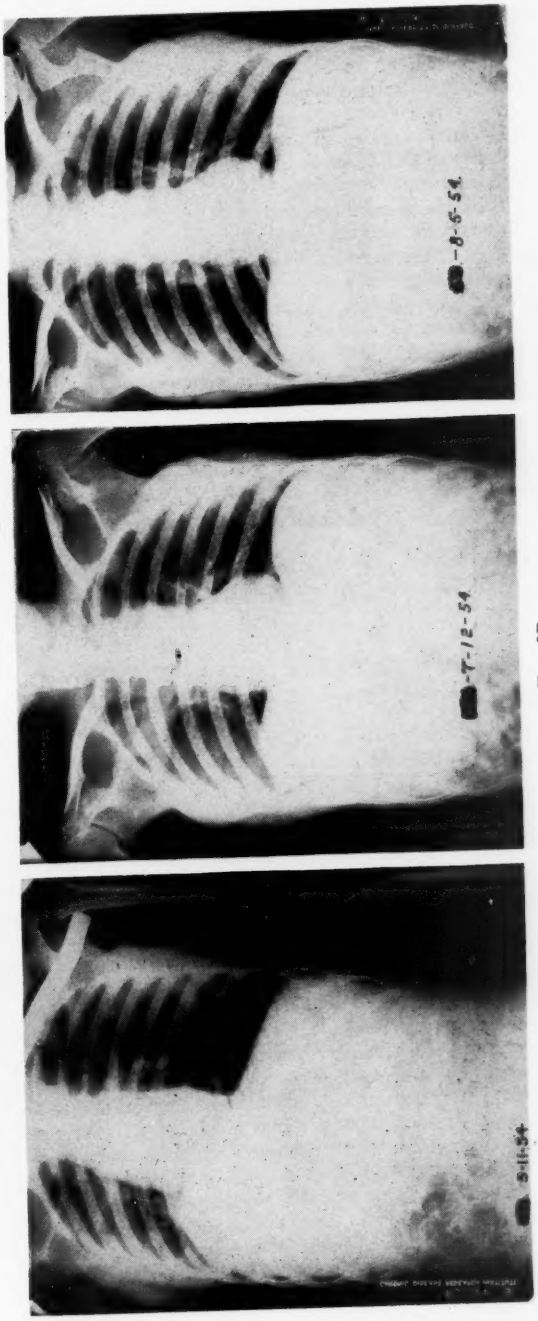

FIG. 9B.

Case 8. This female, age 20, had severe respiratory paralysis affecting all parts of the bellows mechanism. With protracted training of muscle remnants, she attained a vital capacity in the order of 0.4 L. There were no serious respiratory complications, in part because of systematic hyperinflation with positive pressure and manual thoracic stretching.

Case 9. Nearly total respiratory paralysis in this female, age 15, confined the unassisted vital capacity to 0.15 L. or less, yet there were no obstructive complications while she was under treatment.

Case 10. This female patient, age 16, experienced several attacks of atelectasis in the right lung during the acute stage of poliomyelitis and came to us with total respiratory paralysis. There were hazy shadows in the upper half of the right lung field on the chest roentgenogram.

She was one of the first patients in whom we attempted to measure Compliance Volume and treat mucus obstruction with therapeutic cough. Salient features of this instructive experience, together with the illuminating clinical course after returning home and the necropsy findings, support certain premises anticipated in earlier studies

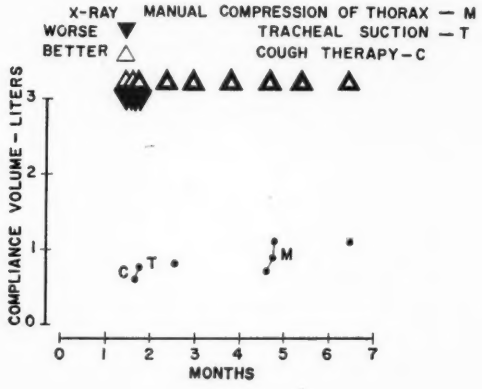

FIG. 9C.

of ventilatory mechanics, particularly with relation to the etiology of anatomic emphysema.

While at the Buffalo Respirator Center the patient contracted an acute respiratory infection and the entire right lung became obstructed with mucopurulent secretions (film of April 30, 1954, figure 9). In addition to the usual measures, she was treated with therapeutic cough *several times a day* without altering Compliance Volume, which was extremely low, 0.6 L., suggesting the limited amount of lung accessible to ventilation, even for a person of small stature. The roentgenograms for several days showed a variable appearance; three of them were improved and four worse. On May 3, 1954, roentgenogram A, the patient was placed on a program of treatment which included an hourly schedule of 15 minutes of inhalation therapy with bronchodilator and Alevaire at pressure of 15 cm. water by a demand valve cycled with the tank respirator, which was set at a negative pressure of 25 cm. water. The dynamic inflation pressure was thus 40 cm. water. This was followed by 15 minutes of cough therapy, with a static insufflation pressure as high as 50 cm. water. Treatment was followed by 30 minutes of rest. After 10 hours there was some inflation of the

midportion of the lung (of May 3, 1954, B), and a small increase in Compliance Volume. Next day there was a discouraging return of the airless state throughout the right lung. Since it was felt that cough could not be expected to open these segments when all the small airways were probably plugged and the parenchyma was airless, the treatment of choice seemed to be direct suction. Tracheotomy was established and catheter suction performed as in case 2. Characteristically, there were no secretions in trachea or major bronchi except during transit from smaller tributaries, which were systematically aspirated with a thin-walled plastic catheter. The mid and lower portion of the right lung immediately inflated (x-ray of May 11, 1954). (Compliance Volume was not measured at that time.) The efficacy of catheter suction was attested by persistent atelectasis in inaccessible apical segments (x-ray of May 12, 1954,) which remained unaltered for nearly three months, until the physical therapist began repeated daily compression to the upper portion of the right hemithorax. The right upper lobe thereupon resumed ventilation, as reflected in the greater Compliance Volume, and by x-ray of August 5, 1954.

The patient returned home with all lobes ventilated under mechanical assistance, her own capacity to breathe being nil. With positive pressure devices, particularly the hand bellows operated by trained companions, this charming but unfortunate young lady enjoyed a variety of the activities which her normal sisters take for granted. She even went on "dates." But the far more exacting requirement for bronchopulmonary cleansing could not be met when she developed acute bronchitis, and more than a year after discharge she succumbed under circumstances which illuminate some of the mechanical principles concerned in lung distention. Chest roentgenograms taken during the terminal illness indicated the presence of massive but shifting atelectatic areas in both lungs. In the earlier attack only the right lung was affected.

Therapeutic cough was not employed, but there was repeated recourse to bronchoscopic aspiration. To provide adequate tidal inflation a combination of positive pressure devices and the tank respirator gave dynamic pressures as high as 50 cm. water. Bilateral spontaneous pneumothorax resulted. On neither side was catheter aspiration of the pleural space able to cope with pleural leakage. At necropsy the posterior, dependent parts of the lungs were atelectatic, but inflation pressures of only 10 mm. Hg, applied for several minutes at a time, reinflated all atelectatic areas promptly. This was a surprising finding, but it illustrates the inverse relationship between time and pressure for penetrating airless parenchyma. Interstitial emphysema was present in the form of perivascular and subpleural accumulations of air, several of the latter being immediately visible on initial inspection of the undisturbed organs. The atelectatic parenchyma which had been reinflated after death showed a hyaline membrane. Diffuse but limited breakdown of alveolar walls could be traced through serial sections in some areas. In all lobes there were numerous small traumatic bullae (largest diameter, 2 cm.; usually less than 1 cm.). These were partly or entirely filled with blood, apart from which they precisely resembled those observed in excised overdistended, tuberculous lungs of guinea pigs. The course of events before death, the stress imposed and the resulting structural alteration probably exemplify at quickened tempo the pathogenesis of anatomic emphysema.

Case 11. This female, age 24, came to us with severe respiratory paralysis from poliomyelitis. Unassisted tidal volume was essentially nil. With the use of positive pressure, particularly glossopharyngeal breathing, the inspiratory range of movement was increased. There were no complications from atelectasis.

Case 12. This male, age 55, had Guillain-Barré syndrome and suffered extreme paralysis of the extremities, moderate weakness of the abdominal muscles and complete loss of diaphragmatic function. The chest wall, especially the upper portion, moved amply, often violently. Respiratory excursion of the abdomen was paradoxic

to that of the chest (figure 10). As one would expect, his ventilation was most limited when the weight of the abdominal organs bore on the flaccid diaphragm in the supine position (figure 11). Pneumotachograph analysis showed in detail the predominant inspiratory weakness and the effect of posture on the failing element in the breathing bellows (figure 12). During convalescence from bilateral basal atelectasis, this patient retained a vital capacity of 1.2 L. in the sitting position, again

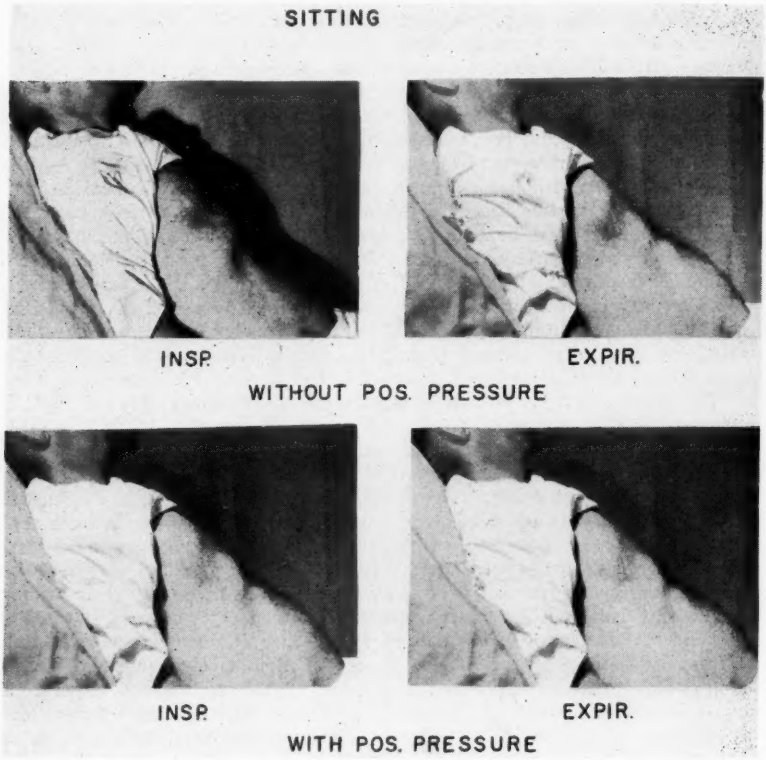

FIG. 10. Thoraco-abdominal antagonism in diaphragmatic paralysis (Case 12). Inspiratory movement of the powerful thoracic wall causes paralyzed diaphragm to move paradoxically; the belly "caves in," even in the nearly-erect position. When supine the phenomenon is more marked. The more forceful the effort to breathe, the greater the paradoxic movement.

emphasizing the serious dysfunction resulting from incomplete enclosure, even when the over-all ventilatory excursion might be considered adequate. Positive pressure breathing dispelled paradoxic movement of the belly wall and restored more even distribution of air. Cough therapy aided in the expulsion of secretions. In a subsequent exacerbation, paralysis extended to the thoracic and abdominal wall. Bulbar involvement led to inspiratory collapse of the pharynx. Tracheotomy had to be performed. Vital capacity fell to .2 L., unaffected by posture.

Summary

Investigation of atelectasis illuminates one facet of a broader function, that of maintaining an adequate rate and distribution of ventilatory flow. This, in turn, is essentially a physical process which must conform to the laws of mechanics and hydraulics. In the present study we have analyzed these principles in relation to atelectasis and find that they correlate well with the clinical manifestations observed in a group of patients prone to develop the

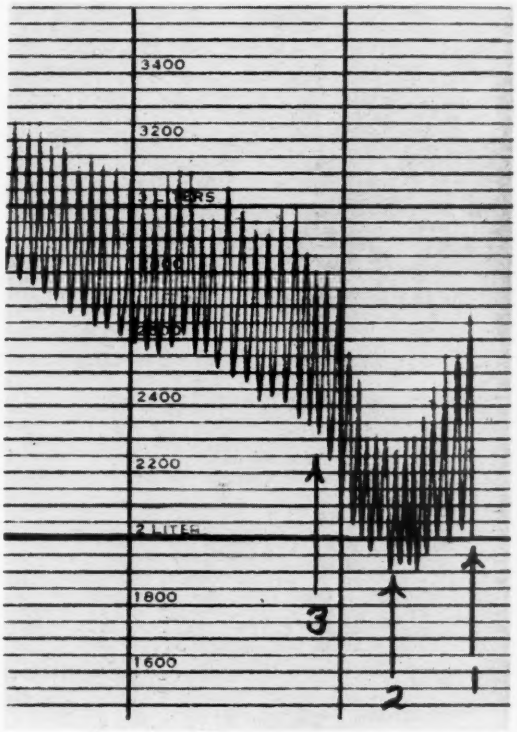

FIG. 11. The effect of gravity on tidal volume in the presence of diaphragmatic paralysis (see text). 1–2 bed lowered; 2–3 bed elevated. Case 12, 8-7-56.

complication. This approach enables one to trace physical factors operative in pathogenesis, to outline therapeutic principles and, in certain instances, to make concrete suggestions for treatment.

Failure of the breathing bellows is the primary mechanical defect, whether the origin be neurochemical or an alteration of structures enclosing the lungs. The immediate and dominant effect is *limitation of inspiratory*

SUPINE
$\dot{V}_P$ = .5L/SEC.
MAX. INSP.
$\dot{V}_P$ = .3 L/SEC.
QUIET BREATHING
$\dot{V}_P$ = .5L/SEC.
$\dot{V}_{POC}$ = .3L/SEC.
COUGH
CASE J.T. 8-7-56
$\dot{V}_P$ = .4L/SEC.
MAX. EXPIR.
ERECT
INSP $\dot{V}_P$ = .35 L/ SEC.
EXP $\dot{V}_P$ = .5 L/ SEC.
QUIET BREATHING
$\dot{V}_P$ = 2.6 L/SEC.
POC ABSENT
MAX. EXPIR.
$\dot{V}_P$ = 1.2 L/SEC.
MAX. INSP.
$\dot{V}_P$ = 3.2 L/SEC.
$\dot{V}_{POC}$ = 1.0L/SEC.
COUGH
CASE J.T. 8-7-56

dynamic pressure which normally dilates intrathoracic airways, as well as causes inspiratory flow. Applied without limit, this pressure could, in theory, by-pass any obstructing agent of fixed dimensions, or it could force an inspiratory passage no matter how firm or how narrow the stricture. A high gradient for inspiratory pressure merely establishes the normal conditions for rapid flow which in health terminates at the position of maximum inspiration (PMI), thereby averting trauma to the lungs. Properties of adhesiveness and a semiliquid state enable mucus and clotted blood to conform to any prevailing shape or diameter of the airway, and thereby to obstruct it during inspiratory flow, the factor essential for development of atelectasis.

Static pressure has to do with *maintaining* pulmonary distention rather than with creating flow. It must be confined within the limits which parenchyma can tolerate without rupture, and it is a relatively small force with which to penetrate a blocked sector of lung. Without knowing the proportion of parenchyma accessible to distention or its structural integrity, it is virtually impossible for the clinician to judge the stress imposed or the strain sustained when lung is inflated by artificial means. These considerations of safe *static pressure* restrict the dynamic pressures which can be therapeutically applied with current devices. Nevertheless, the use of high inspiratory gradients, terminated short of parenchymal rupture, is unequivocally correct in theory, and the therapeutic results in atelectasis of infants support the conclusion in practice. Regardless of the prevailing conditions of pressure against which it must operate, a respiratory aid should be able

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FIG. 12. Pneumotachograph in diaphragmatic paralysis. Flow recorded by measuring gradient in breathing tube across a 400 mesh Monel metal screen by means of Statham transducer P 97, and a Sanborn amplifier-recorder.

Amplification for Quiet Breathing is five times that of other tracings in erect position.

ERECT—60° from horizontal.

Quiet Breathing—Erratic flow due in part to heart beat, dwindling expiratory flow characteristic of passive expiration in patients obliged to ventilate at small lung volume.

Maximal Inspiration—Poor peak flow (V_P)—normal would be 4 L. per second or better. Dwindling terminal flow marks progressive failure of ventilatory muscle as thorax becomes larger.

Maximal Expiration—Volume small, peak flow approximately one-half normal. Flow is erratic. Survey of this and comparable tracings for this patient show no Point of Closure (POC). Expiratory force is weak, due largely to paretic belly wall.

Cough—Coöperation limited by patient's anxiety. Note that flow at point of closure (V_{POC}) varies inversely with peak flow (V_P) and rate of acceleration for successive coughs. This is a feature of intrinsic obstruction in the smaller airways, and in the present instance is probably due to mucus. Despite these variables, and the fact that he was ventilating near the expiratory terminus of the vital capacity, comparable expiratory efforts show that V_{POC} varies inversely with lung volume. The patient does retain Lung Tension (12).

Supine—These four tracings had to be made at the higher amplification. In the supine position inspiratory flow and volume are markedly restricted. He had little inspiratory reserve beyond that employed for quiet breathing. In all tracings of Maximal Expiration there is an abrupt decline following Peak Flow (V_P), and thereafter a slower deceleration of leakage flow. This angle is known as POC. POC could probably be elicited more easily in the supine position, since the smaller lungs would have narrower airways, and contraction of the belly muscles would be enhanced by gravity.

Expiratory weakness of the abdominal muscles is demonstrable in these tracings but overshadowed by the pronounced inspiratory failure of the diaphragm.

to deliver rates of inspiratory flow in the order of 4 L. per second for the treatment of atelectasis. Most devices in present use cannot do this, being scaled to resting ventilatory need.

Breathing at a small functional reserve volume increases resistance to flow and renders the narrow airways more vulnerable to obstruction. Kinetic energy available for passive expiration is likewise diminished. Effective cough requires active, often violent participation of voluntary muscles to provide the force necessary to narrow cartilaginous airways and to create the high linear velocity needed to sweep secretions from them. High volume flow alone cannot provide the requisite physical conditions.

Disproportionate weakness of a *part* of the breathing bellows predisposes the patient to atelectasis more than does over-all insufficiency. Paradoxic ventilation (flow from one segment of lung to another) explains this vulnerability to atelectasis for lung underlying the weaker portion. It is therapeutically advantageous to gauge the respective capacity of the parts, costal wall, diaphragm and belly wall. Disparity can be corrected by invoking the aid of gravity and by proper adjustment of abdominal supports and spinal braces. At times such simple measures in themselves can reëstablish adequate unassisted resting ventilation.

Of the respiratory aids, only the tank respirator and positive pressure devices can potentially provide equal distribution of air to all lung segments. The latter is more adaptable to the varied requirements of daily living for patients with chronic ventilatory weakness. Positive pressure breathing devices can be employed in a great variety of body positions and can stretch component parts of the ventilatory system and thereby restore a more normal range of flexibility which, in turn, enhances the effective use of whatever capacity the patient may retain for unassisted breathing. They have the added practical advantage of simple construction and control, which can enable the patient to regulate tidal volume and frequency. We have not observed circulatory embarrassment due to positive pressure breathing in patients with chronic respiratory paralysis, but this does not resolve the question for those in whom the circulatory condition is more precarious. If one suspected that a mean supra-ambient intrathoracic pressure threatened the pulmonary circulation, it would be easy to adjust most of the devices to positive-negative pressure breathing, although we were not aware of a need for doing so in the cases here reported. Cough is a vital therapeutic measure. When the bellows mechanism is deranged, so that cough does not effectively clear secretions from the airway system or from a portion thereof, the natural function must be supplemented or replaced by artificial means. Devices for this purpose should simulate the frequency, pressure and flow characteristics of natural cough.

Therapeutic cough, so employed, is immediately and demonstrably effective for expelling secretions as long as the distal parenchyma still contains air. The prime indication is *prevention* of atelectasis. When the paren-

chyma has become airless, cough per se is not so effective, but it should be used in conjunction with direct suction to obstructed tributaries. These conclusions apply in failure of the bellows mechanism. Obstructive conditions such as bronchial asthma are not considered in this report.

Our investigations suggest that a mechanical device to simulate the condition of natural cough should have separate insufflation and exsufflation systems except where they unite at the mouth. This prevents rebreathing and cross-infection, besides facilitating accurate control of flow and pressure. The Cough Caddy is a device which embodies a number of these desirable features. It measures Compliance Volume, the amount of air which can be returned after insufflation to a given static pressure. Compliance Volume is dependent upon a number of variables, such as stature, bellows flexibility, and capacity for unassisted breathing. Abrupt changes reflect alteration in the amount of lung accessible to ventilation. A sharp drop in Compliance Volume signifies impending atelectasis even before it becomes roentgenographically demonstrable. Compliance Volume instantly increases when obstructing secretions are successfully expelled by therapeutic cough.

Summario in Interlingua

Le stato de absentia de aere in atelectasis es precedite per un stato in que le pulmones es replenate sed in que nulle ventilation aeree es effectuate a causa del obstruction bronchial que es usualmente causate per muco o sanguine. Il ha quatro factores governante in le etiologia de iste condition:

1. Le volumine de aere que pote esser displaciate.
2. Le elasticitate del tension pulmonar que varia con le volumine del pulmones e del vias aeree in general.
3. Le diametro del vias aeree.
4. Le pression del mechanismo respiratori que propelle le aere e depende del altere factores mentionate.

Dysfunction mechanic limita le replenation inspiratori, reduce le energia cinetic del expiration, e impone un alte resistentia al fluxo intra le restringite vias aeree. Le plus serie situation resulta quando un parte del mechanismo es plus inefficace que le resto, de maniera que il ha ventilation cruciate intra le pulmones. Atelectasis se disveloppa infra le portion inefficace del apparatura.

Correspondentemente, le tractamento debe visar a effectuar un distribution uniforme de aere. Isto pote esser obtenite solmente per le application de un pression positive al interior del vias respiratori o per le uso de un respirator que include le corpore integre e assi certemente omne le partes de illo que es expansibile. Ante le stadio del absentia de aere, le production de tusse therapeutic es multo efficace. Pro iste objectivo un pumpa bi-canalate esseva disveloppate que non solmente applica le tractamento sed etiam mesura le resultato. In le stadio de absentia de aere, directe suction applicate al vias aeree es un indispensabile mesura preliminar. Le theoria dynamic justifica clarmente le uso de alte pressiones inspiratori, terminate proxime al limine de ruptura parenchymal. Disequilibrio del fortias mechanic pote esser corrigite sub certe conditiones per le application de un cinctura abdominal e le adjustation del position del corpore. Iste conceptos se trova de accordo con le experientia clinic.

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A CLINICOPATHOLOGIC STUDY OF CHRONIC RENAL VEIN THROMBOSIS IN ADULTS*

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INTRODUCTION

THIS report is based on a clinical and pathologic study of six cases of bilateral renal vein thrombosis in adults. Current interest in this entity has been reflected by an increasing number of case reports in the last several years.[1-9] This interest is stimulated by the associated nephrotic syndrome occurring in cases of renal vein thrombosis. The mechanism for the development of renal vein thrombi is poorly understood, as is the genesis of the nephrotic syndrome. In infants, acute renal vein thrombosis associated with diarrhea and dehydration is a relatively common occurrence. The rapid clinical course is associated with lumbar pain and tenderness, hematuria, azotemia and shock. Anatomically, the kidneys exhibit massive hemorrhagic infarction. In adults, on the other hand, the diseases which appear to predispose to chronic renal vein thrombosis vary, and include compression or invasion of the renal veins by a malignant neoplasm, multiple venous thrombi, diffuse vascular disease, renal amyloidosis and congestive heart failure.[10] The clinical course may be prolonged, and the anatomic reflection of renal vein occlusion within the parenchyma of the kidney may be variable. In some cases, a full-blown nephrotic syndrome has been associated with meager changes in the kidneys, such as interstitial edema. In others, interstitial fibrosis and tubular atrophy have been noted. Significant glomerular changes have recently been described for the first time in a case followed during life by serial renal biopsies.[9]

Four of our cases exhibited a nephrotic syndrome attributable only to chronic renal vein thrombosis. The other two cases were complicated by diabetic glomerulosclerosis and renal amyloidosis, respectively. The nephrotic syndrome in these two cases could have been explained by the coexisting renal disease without invoking the rôle of chronic renal vein thrombosis.

CASE REPORTS

Case 1. The patient, a 39 year old white female, was admitted to Montefiore Hospital on October 13, 1952, because of increasing dyspnea. She had had acute

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arthritis involving both ankle joints at the age of 20 years. At 29 years of age she had been told that she had a cardiac murmur which was due to rheumatic heart disease. Seven years prior to admission she began to have manifest dyspnea, orthopnea and peripheral edema, which responded to digitalization, mercurial injections and a low salt diet. Two years before hospitalization she suffered the sudden onset of chest pain with hemoptysis and fever. A chest x-ray confirmed the clinical diagnosis of an acute pulmonary infarct. The patient had been hospitalized elsewhere three months prior to the present admission. The significant findings consisted of marked peripheral edema and right pleural effusion. There was cardiac enlargement associated with a short presystolic apical murmur and a high-pitched basal diastolic murmur. The liver was enlarged four fingerbreadths below the right costal margin. The venous pressure, however, was 50 mm., with a rise to 60 mm. on right upper quadrant pressure. The Decholin circulation time was 18 seconds. The urine concentrated to a specific gravity of 1.030 and revealed a persistent 4 plus albuminuria. This was quantitated and varied from 4 to 6 gm. per 24 hours. The blood urea nitrogen was 12 mg.%. The total serum protein was 5.2 gm.%, with an albumin of 2.2 and a globulin of 3.0 gm.%. The total cholesterol was 900 mg.%. The Congo red test revealed 60% retention. An x-ray of the chest confirmed the presence of a large right pleural effusion. Oblique views demonstrated an enlarged left auricle. An intravenous pyelogram showed good visualization, with no abnormalities. An electrocardiogram showed auriculoventricular block with frequent dropped beats. The patient was treated with a low salt diet and frequent mercurial injections, with a marked decrease in peripheral edema. She was transferred to Montefiore Hospital.

Studies revealed almost identical findings to those described above. The venous pressure and Decholin and ether circulation times remained within normal limits. The urine contained 10 to 12 gm. of protein per 24 hours. The specific gravity was 1.024, and examination of the urinary sediment revealed an occasional red blood cell and white blood cell but no casts. The total cholesterol values ranged from 400 to 600 mg.%, with esters ranging from 350 to 450 mg.%. The urea clearance was 30% of normal. Repeated studies of fluid from the right pleural cavity for tumor cells, pyogenic organisms and tubercle bacilli were negative.

Because of the repeated normal hemodynamic studies, it was considered that the marked peripheral edema and right pleural effusion were not due to congestive heart failure, although clinically the patient was considered to have rheumatic heart disease. Digitalis was administered to the point of toxicity, and mercurials were administered frequently, with no mobilization of the edema. Repeated pleural taps were required because of the rapidity of reaccumulating pleural effusion. The patient became increasingly lethargic, and died with acute pulmonary edema on January 27, 1953.

Necropsy: Final Anatomic Diagnosis: A. Healed rheumatic mitral, tricuspid and minimal aortic valvulitis; thrombus on mitral valve leaflet; dilatation and hypertrophy of left auricle and right ventricle; infarct in right kidney; chronic passive congestion of lungs, liver and spleen; right pleural effusion and adhesions; bilateral edema of lower extremities. B. Organizing thrombi in both renal, left ovarian and left adrenal veins; interstitial fibrosis and tubular atrophy in kidneys.

The right kidney weighed 120 gm. and was 10 by 5.5 by 3 cm. in its greatest dimensions. The left kidney weighed 130 gm. and measured 10.5 by 6.5 by 3 cm. Both main renal veins were completely occluded by light tan thrombi which extended from the renal vein ostia in the inferior vena cava into and including the renal vein radicles in the peripelvic fat and within the renal substance (figure 1).

The surfaces of both kidneys were smooth and dark red. The cut surfaces exhibited cortices of normal width and distinct striations. The cortices were diffusely stippled by punctate areas of yellow discoloration. There was a small, fresh infarct in the right kidney measuring 2.0 cm. in greatest diameter.

FIG. 1. *Case 1.* Organizing thrombi in both renal, left ovarian and left adrenal veins.

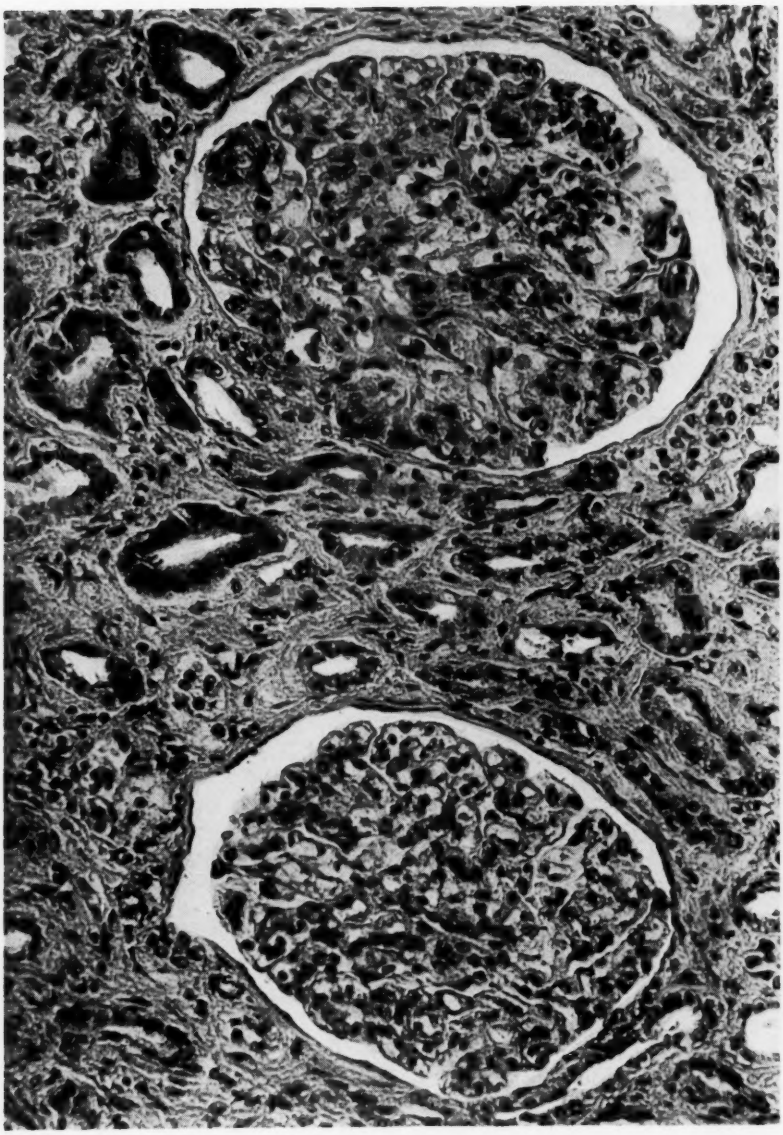

FIG. 2. *Case 1.* Area of interstitial fibrosis and tubular atrophy. Masson stain; × 210.

FIG. 2. *Case 1.* Area of interstitial fibrosis and tubular atrophy. Masson stain; × 210.

FIG. 3. *Case 1.* Mild thickening of glomerular capillary basement membranes in area of interstitial fibrosis and tubular atrophy. Periodic acid-Schiff stain; × 210.

Microscopically, the thrombi were hyalinized and exhibited organization by proliferated fibroblasts and capillaries around the peripheral areas. Organization was more advanced in the vein radicles than in the main renal veins. The renal parenchyma was marked by widespread zones of interstitial fibrosis with tubular atrophy (figure 2). The glomeruli in the zones of interstitial fibrosis exhibited mild thickening of the capillary basement membranes (figure 3). Sudanophilic fat was demonstrated in the epithelium of the proximal convoluted tubules as well as in tubular casts. Under polarized light, doubly refractile lipoid bodies were visualized in the same structures.

Comment: The clinical picture of congestive heart failure due to rheumatic heart disease was reflected by the autopsy findings. In addition, organizing occlusive thrombi were present in both renal veins. A nephrotic syndrome existed during life. Large areas of interstitial fibrosis with tubular atrophy were found at autopsy in the kidneys. The glomeruli in these areas showed mild thickening of the capillary basement membranes. This represents a clinicopathologic pattern that has been previously described in chronic renal vein thrombosis.

Case 2. The patient, a 45 year old male, was admitted to Montefiore Hospital on March 13, 1931, because of increasing peripheral edema and right hydrothorax.

A year and a half prior to admission he had had the sudden onset of pain in the right costovertebral angle which radiated along the course of the right ureter and into the right testicle. An intravenous pyelogram revealed good visualization of both kidneys. No calculi or other abnormalities were demonstrated. The patient was put to bed for two weeks, with eventual subsidence of the pain. He had suffered a similar episode of lumbar pain five years prior to admission. Hypertension associated with 4 plus albuminuria was noted for the first time six months prior to admission. A progressive weight loss of 30 pounds was noted in the year prior to admission. The effusion in the right pleural cavity was tapped prior to admission and was found to be chylous fluid.

Physical examination revealed a dyspneic middle aged male with marked periorbital puffy edema. The blood pressure was 170/110 mm. of Hg; pulse rate, 80 and regular. The point of maximal impulse was in the fifth intercostal space in the anterior axillary line. A split first sound was heard at the apex, with a soft systolic murmur heard over the entire precordium. The lungs revealed dullness, with absent breath sounds on the right side. The liver edge was palpable four fingerbreadths below the right costal margin. The spleen was not felt. There was 4 plus pitting edema of both lower extremities extending up to the midthigh area. There was marked sacral edema.

Examination of the urine revealed a specific gravity of 1.018 to 1.022. There was a persistent 4 plus albuminuria, and the urinary sediment revealed granular and hyaline casts and occasional white blood cells, with no red blood cells. Numerous doubly refractile cells and casts were noted. These were studied by means of polarized light and typical Maltese crosses were described. The urine was quantitated for albumin, and this varied from 18 to 20 gm. per 24 hours. The hemoglobin varied from 11.2 to 12.8 gm., with a red blood cell count of 4,000,000. The white blood cell count varied from 6,200 to 11,000, with a normal differential count. The fasting blood sugar and blood urea nitrogen were 96 and 14 mg.%, respectively. The total serum cholesterol measured 548 mg.%. The total serum protein measured 4.5 gm.%, with an albumin of 1.7 and a globulin of 2.8 gm.%. The serum calcium and phosphorus measured 8.2 and 6.0 mg.%, respectively. The basal metabolism rate was

plus 11. An electrocardiogram revealed evidence of left ventricular strain. A chest x-ray showed a large pleural effusion extending up to the third rib, displacing the heart to the left. There was marked left and right ventricular enlargement. An intravenous pyelogram again revealed good function bilaterally, with no abnormalities.

The patient exhibited a low grade febrile course. A thoracentesis on admission revealed a chylous fluid which showed mesothelial cells, lymphocytes, and a few polymorphonuclear leukocytes on microscopic examination. No doubly refractile lipoid bodies were seen upon examination of fluid smears under polarized light. A moderate amount of neutral fat was seen. No tumor cells were found. Originally, congestive heart failure was considered the underlying disease, but in view of the severe albuminuria and the characteristic urinary sediment, it was felt that a nephrotic syndrome was the prime clinical consideration. A Congo red test revealed no retention of dye, and chronic glomerulonephritis was considered the most likely cause of the nephrotic syndrome. The patient was placed in the metabolic ward and was treated with ammonium nitrate, Salyrgan and urea, which resulted in a weight loss of 22 pounds. It was possible to keep the patient almost edema-free under this regimen, with the weight varying from 125 to 130 pounds. After extensive diuresis it was noted that there was moderate distention of the superficial veins of the chest and periumbilical region. Liver function studies, including bromsulfalein excretion, icteric index and serum bilirubin levels, were normal. In view of these findings, and in the absence of overt congestive heart failure, the hepatomegaly and the abdominal collateral venous circulation were attributed to cirrhosis or to adhesions around the inferior vena cava just below the diaphragm. Freely bleeding internal hemorrhoids developed, resulting in a marked drop in blood hemoglobin levels, which necessitated several blood transfusions. On January 25, 1932, the patient suddenly went into shock and died.

Necropsy: Final Anatomic Diagnosis: A. Organized thrombi with recanalization in renal veins, inferior vena cava, right and left common and external iliac veins, left internal iliac vein, testicular veins and left adrenal vein, interstitial fibrosis with tubular atrophy and thickening of glomerular capillary basement membranes in kidneys; pleural adhesions, encapsulated chylothorax in base of right pleural cavity, atelectasis of right lower lobe of lung, focal pneumonia. B. Coronary arteriosclerosis with old occlusion of anterior descending branch of left coronary artery, healed infarct of anterior wall of left ventricle.

The right kidney weighed 170 gm. and measured 12 by 6 by 3.5 cm. The left kidney weighed 180 gm. and measured 13 by 5.5 by 3.5 cm.

Both main renal veins were occluded by organized and recanalized thrombi which were firm, translucent and gray. The cut surfaces of the thrombi were porous, due to the presence of recanalized channels. The thrombi extended into the smaller radicles of the main veins in the peripelvic fat and in the substance of the kidneys. The thrombus in the left renal vein was continuous with similar thrombi in the left testicular and adrenal vein and with a thin band of organized firm, gray-brown thrombus adherent to the anterior wall of the inferior vena cava. The thin, bandlike thrombus in the inferior vena cava measured 0.5 to 0.8 cm. in width and extended from a level 5 cm. above the renal vein ostia down to the bifurcation of the inferior vena cava, where it was continuous with thrombi occluding the common and external iliac veins bilaterally and the left internal iliac vein. The thrombi in these vessels were similar to those found in the renal veins but showed fewer recanalizing channels. The thrombus in the inferior vena cava was separate from the one found in the right renal vein but was continuous with the thrombus in the right testicular vein.

The blood vessels in the perirenal fat were prominent, dilated and congested. The stellate veins of the renal capsule were unusually prominent and congested. The capsule of the kidney could be stripped easily to reveal injected yellow, smooth sur-

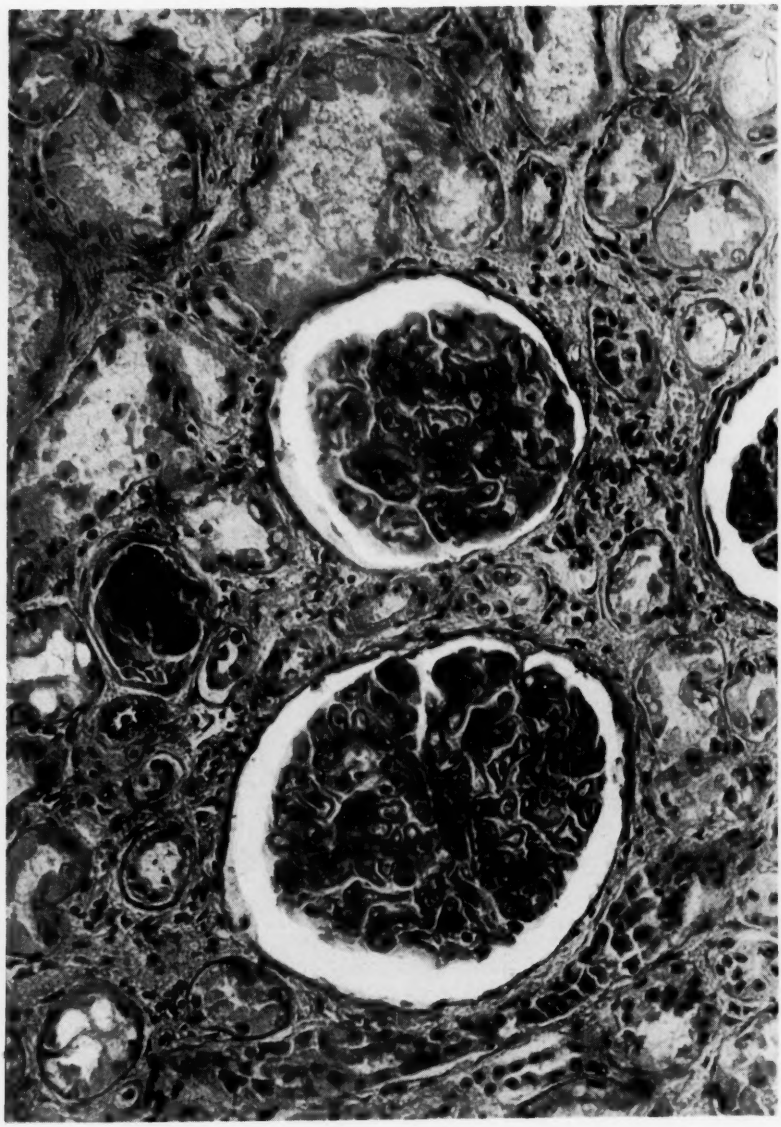

FIG. 4. *Case 2.* Thickening of glomerular capillary basement membranes, interstitial fibrosis and tubular atrophy. Periodic acid-Schiff stain; ×210.

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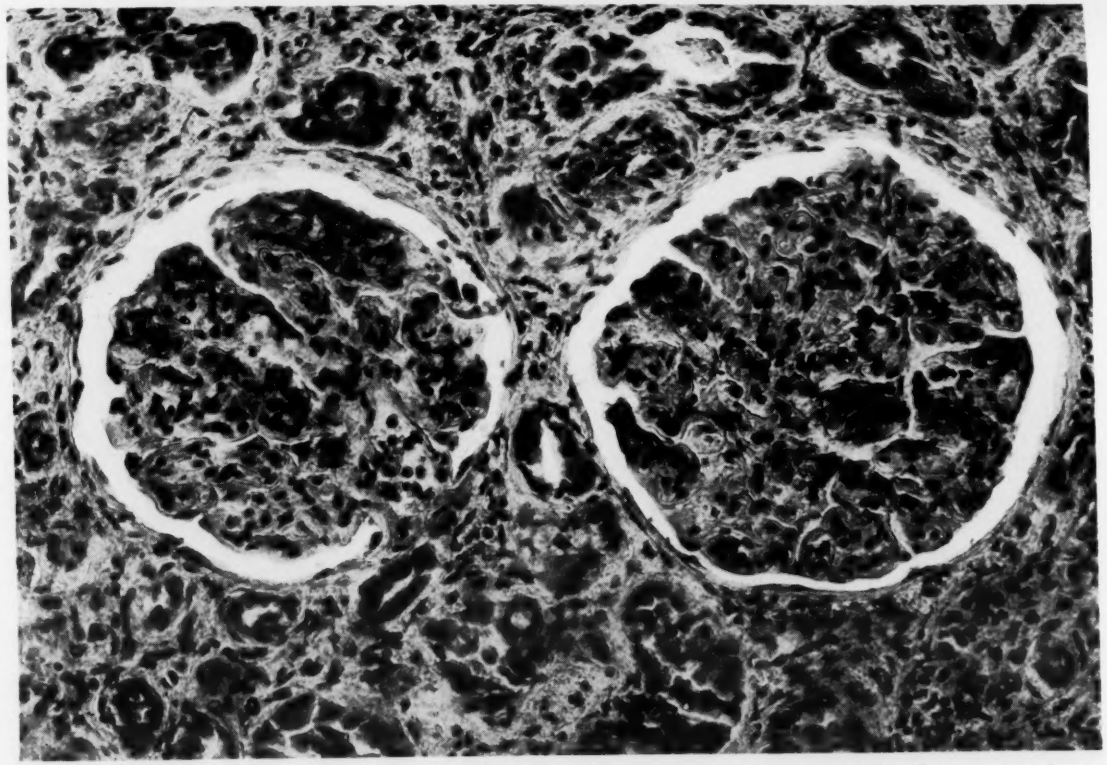

FIG. 5. *Case 2.* Interstitial fibrosis and tubular atrophy. Thickening of the glomerular capillary basement membranes is also evident. Masson stain; × 210.

faces with preserved fetal lobulations. The kidneys cut with increased resistance, and showed pale yellow cortices which contrasted with the red medullae. The cortices were streaked and stippled by numerous closely packed, minute foci of yellow discoloration.

Histologically, the thrombi in the renal veins were completely organized and replaced by a sparsely cellular, loose fibrous tissue containing numerous large channels of recanalization which were concentrated mainly around the periphery. The walls of the veins were thickened by fibrous tissue and showed no inflammatory cellular exudate.

All of the glomeruli showed a strikingly uniform thickening of the basement membranes with a mildly increased cellularity (figure 4). There was a diffuse interstitial fibrosis in the cortex and medulla with tubular atrophy (figure 5). Occasional tubules were dilated and contained hyaline or granular casts. Occasional small linear scars due to arteriosclerosis were seen in the cortex, and contained a few atrophic tubules and hyalinized glomeruli with an exudate of round cells. There was no evidence of arteriolar nephrosclerosis. Sections stained with Sudan III revealed extensive deposition of neutral fats, predominantly in the epithelial cells of the proximal convoluted tubules. Suitable tissue was not available for examination for doubly refractile lipoid bodies.

Comment: None of the usual predisposing causes of thrombosis of the renal veins existed in this case. The relatively long duration of a nephrotic syndrome was reflected at autopsy by the complete organization with recanalization of the thrombi. There were diffuse renal tubular atrophy and interstitial fibrosis. The presence of distinct diffuse thickening of the basement membranes of the glomerular capillaries was equally striking. Until now, this change has been reported but once in association with chronic renal vein thrombosis.[9]

Case 3. The patient, a 56 year old white female, was re-admitted on August 2, 1952, because of a pathologic fracture of the right femur. She had been apparently well until two years prior to the present admission, when she developed exquisite pain in the left knee. An x-ray showed a destructive process involving the left patella. A left patellectomy was performed in August, 1951. The pathologic diagnosis was metastatic anaplastic carcinoma. A primary site was not determined at this time. One month later, however, a right axillary node became palpable. This was excised for biopsy and also revealed metastatic anaplastic carcinoma. A thorough physical and roentgenographic examination was unrewarding in the determination of the primary site. In January, 1952, a mass became palpable in the right breast for the first time after numerous previous examinations by several physicians. The patient was treated with various hormonal combinations, which had no effect on progressive enlargement of the mass in the right breast, with metastases to the opposite breast, cervical lymph nodes and to the skeletal system. Bilateral pleural effusions developed in February, 1952. She developed a pathologic fracture of the right femur in August, 1952. A pathologic fracture of the left femur occurred in December, 1952, and was treated with radiotherapy, with relief of pain.

On April 12, 1953, massive edema was noticed below the waist for the first time. Four plus albuminuria was consistently present in every specimen, in contrast to the absence of albuminuria in previous urinalyses. The urinary sediment contained many fresh white blood cells. Red blood cell casts were not observed. The blood urea nitrogen, which had previously been in the range of 18 to 20 mg.%, rose to 60 mg.%. The serum creatinine rose to 4.5 mg.% from a previous level of 0.8 mg.%. The

serum protein was 6.6 gm.%, with a serum albumin of 3.7 and a serum globulin of 2.9 gm.%.

The patient became increasingly oliguric and became anuric within a week. The most likely diagnosis in view of the edema and increasing albuminuria was obstruction of the inferior vena cava with bilateral renal vein obstruction by tumor thrombi. Because of the possibility of bilateral ureteral obstruction by metastatic neoplastic tissue, ureteral catheters were passed. No obstruction was observed. The anuria persisted. On April 20, 1953, the patient died.

Necropsy: Final Anatomic Diagnosis: Anaplastic carcinoma of the right breast; scars of left patellectomy and right femoral intramedullary spike insertion for metastatic carcinoma; metastases to left breast, liver, lungs, pancreas, spleen, bone, lymph nodes, peritoneum, adrenal glands, left ureter, uterus, ovaries and right brachial plexus; constriction of inferior vena cava, right renal vein and both renal arteries, with occlusion of left renal vein by retroperitoneal metastases; massive edema of lower extremities and right arm; bilateral pleural effusion.

The kidneys were not weighed; the right and left kidneys measured 10.5 by 5 by 3 and 10.5 by 5.5 by 2.5 cm. in greatest dimensions, respectively. The vascular pedicles of both kidneys as well as the inferior vena cava and aorta were all engulfed by a confluent mass of metastatic anaplastic carcinoma. The left renal vein was completely occluded by the neoplasm, which invaded all layers and filled the lumen. The right renal vein was similarly invaded and was narrowed without complete occlusion. The inferior vena cava was greatly narrowed by the invading and constricting neoplasm, beginning 2 cm. above the renal vein ostia and extending inferiorly for a distance of 6 cm. Both renal arteries were moderately narrowed by enveloping tumor tissue.

The surfaces of both kidneys appeared pale red. The cut surfaces exhibited pallor, with a blurring of cortical striations.

Sections of both renal veins revealed invasion of all layers of their walls by anaplastic carcinoma. The neoplastic tissue virtually filled the lumen of the left renal vein.

Aside from widely scattered small scars, the histologic appearance of the renal parenchyma was not remarkable. A few droplets of sudanophilic fat and an occasional doubly refractile lipoid body were found in the proximal convoluted tubules.

Comment: A terminal nephrotic syndrome of eight days' duration was manifest clinically, due to constrictive invasion of the inferior vena cava and renal veins by metastatic carcinoma. Aside from the deposition of a few droplets of sudanophilic fat and an occasional doubly refractile lipoid body in the tubular epithelium, there was no anatomic alteration within the glomeruli or tubules which reflected occlusion of the renal veins. This might be explained by the short duration of the process.

Case 4. The patient, a 70 year old white female, was admitted on March 23, 1948, because of increasing peripheral edema of six weeks' duration. She had had known diabetes for three years. Eighteen months prior to admission she had developed dyspnea on exertion and orthopnea. One year prior to admission a diagnosis of arteriosclerotic heart disease was made, and she was maintained on a low salt diet, digitalis and occasional mercurial injections. She complained of edema of the lower extremities two months prior to admission, and this had increased in severity over the preceding six weeks. Administration of daily intramuscular injections of Mercuhydrin for the five-day period prior to admission had had no effect on the peripheral edema.

Physical examination revealed a dyspneic and cyanotic female. The pulse rate was 100 and regular. The blood pressure was 100/60 mm. of Hg in each arm. There were bilateral lenticular opacities. Funduscopic examination revealed marked arteriolar changes, with no evidence of diabetic or hypertensive retinopathy. There was a bilateral pleural effusion. A loud, high-pitched systolic murmur was heard at the apex and over the entire precordium. The liver edge was palpable three fingerbreadths below the right costal margin, with a distinct smooth edge. The spleen was not felt. Four plus pitting edema was noted over both lower extremities.

An x-ray of the chest confirmed the presence of fluid in both pleural cavities. The left ventricle was moderately enlarged, and the left auricle was enlarged posteriorly. Outflow tract enlargement of the right ventricle was present. The electrocardiogram revealed left axis deviation, with a left ventricular strain pattern. Urinalysis revealed a persistent 4 plus albuminuria in all random samples, with a specific gravity varying from 1.010 to 1.014. An occasional specimen revealed 1 plus glycosuria. The urinary sediment contained an occasional white blood cell. Red blood cells and hemoglobin casts were not noted. An occasional hyaline and granular cast was seen. Doubly refractile fat bodies were observed in only one specimen. The hemoglobin was 10 gm., with a red blood cell count of 3,500,000. The white blood cell count was 6,000, with a normal differential count. The fasting blood sugar ranged from 110 to 230 mg.%. The blood urea nitrogen varied from 25 to 35 mg.%. The serum creatinine was 2.4 mg.%. The total cholesterol varied from 256 to 321 mg.%. The urea clearance was 57 and 52%, respectively. Quantitative urinary protein excretion varied from 4.5 to 8.0 gm. per 24 hours. The total serum protein was 6.0 gm.%, with a serum albumin of 3.3 and a serum globulin of 2.7 gm.%.

The venous pressure on admission was 120 mm., with a rise to 150 mm. on hepatic pressure. The Decholin circulation time was 19 seconds. Dyspnea and peripheral edema increased in spite of a salt-poor diet, frequent administration of diuretics, and increasing digitalization to the point of toxicity. The patient had a low grade fever which was unaffected by antibiotics. The blood urea nitrogen rose to 65 mg.%. Bilateral pleural effusions re-accumulated with increasing rapidity, requiring frequent thoracenteses. The patient became increasingly azotemic and died on April 4, 1948.

Necropsy: Final Anatomic Diagnosis: Primary: A. Severe generalized arteriosclerosis; calcific aortic stenosis, calcified mitral valve ring, hypertrophy and dilatation of left ventricle; coronary arteriosclerosis, multiple myocardial scars, pericardial adhesions, thrombus in anterior descending branch of left coronary artery, recent infarct of anterior wall of left ventricle and of anterior portion of interventricular septum; atherosclerotic ulceration of aorta with mural thrombus, old splenic and renal infarcts; arteriolar nephrosclerosis; chronic passive congestion of lungs; bilateral pleural effusions; edema of lower extremities; focal pneumonia. B. Organizing thrombi in both renal and ovarian veins, in the inferior vena cava, and in the left adrenal vein. Secondary: Moderate periportal fibrosis in liver; adenoma of thyroid gland.

Each kidney weighed 110 gm. and measured 11 by 6 by 2 cm. in their greatest dimensions. Both main renal veins were occluded by tan thrombi in continuity with a large thrombus in the inferior vena cava. This thrombus extended from a level 2.0 cm. below the renal vein ostia superiorly to the orifice of the inferior vena cava in the right auricle. The thrombus was attached to the anterior wall of the inferior vena cava at the level of the renal veins and did not effectively occlude the inferior vena cava above this level, where it was disposed as a propagated loose "tail." The thrombi in the main renal veins extended into the venous radicles in the peripelvic fat.

The surfaces of both kidneys were finely granular. A healed infarct was found in each kidney, measuring 1.0 and 3.0 cm. in greatest dimension in the right and left

kidneys, respectively. The cortices on section were narrowed to 4 mm. and exhibited a blurring of architectural markings.

Microscopic sections of the main renal veins disclosed organization with recanalization around the peripheral portions of the thrombi. The recanalized zones appeared as large, tortuous, slitlike endothelialized channels. The veins in the peripelvic fat exhibited complete organization with recanalization. The vessel lumens were traversed by fibrous trabeculae lined by endothelium to form numerous irregular channels of recanalization.

The kidneys showed arteriosclerosis and arteriolosclerosis with moderate scarring. In areas free of scarring due to arteriosclerosis, no interstitial fibrosis attributable to renal vein thrombosis was seen. The lesion of intercapillary glomerulosclerosis was not present. Sudan III preparations revealed free fat in the proximal convoluted tubules and in tubular casts. Doubly refractile lipoid bodies were demonstrated.

Comment: Renal vein thrombosis was associated in this case with congestive heart failure. Vascular scars in a pattern reflecting arterial and arteriolar nephrosclerosis were present in the kidneys. Any possible parenchymal changes attributable to renal vein thrombosis could not be identified because of the coexisting renal vascular disease. Although the patient was diabetic, lesions of intercapillary glomerulosclerosis were not found.

Case 5. This 72 year old white male was admitted to Montefiore Hospital on March 3, 1954, because of marked edema of both lower extremities and gangrene of the right leg. The patient had sustained an injury to the right ankle one year previously which had healed spontaneously after two months. Six months prior to admission, edema of the right leg and thigh developed and rapidly became marked, occasioning his admission to another hospital. Examination at that time revealed cardiac enlargement which was chiefly confined to the outflow tract of the left ventricle, as revealed by fluoroscopic and x-ray studies. An electrocardiogram demonstrated a sinus arrhythmia. A report of one urine examination showed 4 plus albuminuria, with the presence of 20 to 25 red blood cells per high power field. The fasting blood sugar and blood urea nitrogen were normal. A diagnosis of thrombosis of the right common iliac vein with possible extension to the inferior vena cava was considered. He was treated with Dicumarol for 10 days. The treatment was discontinued because of the development of gross hematuria. Digitalis and mercurials were administered, with no effect on the leg edema. Edema of the left leg developed during the ensuing few months, followed by gangrene of the edematous right leg, which occasioned his admission to Montefiore Hospital.

Physical examination revealed a blood pressure of 160/90 mm. of Hg. There were bilateral fine basilar râles, and the liver edge was palpable three fingerbreadths below the right costal margin. The femoral and popliteal arterial pulsations were bilaterally palpable, but the dorsalis pedis pulsations on either side were absent. Four plus pitting edema involved both lower extremities and the lower half of the abdominal wall. The right lower extremity was more edematous than the left, and gangrenous ulcers were noted over both the right malleoli and the left heel.

The hemoglobin was 10.5 gm., with a red blood cell count of 3,600,000 and a white blood cell count of 7,500, with a normal differential count. The urine concentrated to a specific gravity of 1.018, with 4 plus albuminuria. Numerous white blood cells were noted per high power field. The fasting blood sugar, blood urea nitrogen and serum creatinine were 238, 67 and 2.0 mg. %, respectively. The total cholesterol was 430 mg. %. The total protein was 4.6 gm. %, with an albumin of 2.8 and a globulin of 1.8 gm. %.

The leg ulcers were treated with debridement and broad spectrum antibiotics.

The gangrene of the right leg continued to spread, and a right midleg amputation was done three weeks after admission. The pathologic findings of the amputated right leg consisted of arteriosclerosis obliterans, with medial calcification and organizing thrombi in the anterior and posterior tibial veins. The postoperative course was relatively uneventful except for persistent albuminuria and glycosuria. Spreading gangrene of the left leg necessitated a left midleg amputation three weeks later. The immediate postoperative course was relatively uneventful, but on the fifth postoperative day, April 25, 1954, the patient died.

Necropsy: Final Anatomic Diagnosis: Primary: A. Generalized arteriosclerosis with particular involvement of peripheral and coronary arteries, myocardial scars; organizing and fresh thrombi in peripheral veins, wounds of guillotine amputation of both legs for gangrene; thrombi in renal veins; emboli in main pulmonary arteries; edema of lower extremities. B. Cirrhosis of liver. Secondary: Adenomatous hyperplasia of thyroid gland; intercapillary glomerulosclerosis.

The kidneys were enlarged and measured approximately 13 by 7 by 3 cm. in their greatest dimensions. Thrombi were present bilaterally in the radicles of the main renal veins in the peripelvic fat and in the substance of the kidneys. These thrombi were continuous with those found in the distal 1 to 2 cm. of both main renal veins. The surfaces of both kidneys were finely granular, and the parenchyma on section appeared edematous, with a blurring of cortical striations and corticomedullary junctions.

The thrombi exhibited early organization around the periphery, as indicated by the presence of scattered fibroblasts. The kidneys showed arteriosclerotic scarring. Rare glomeruli were involved by the typical lesion of diabetic glomerulosclerosis. In unstained frozen sections, doubly refractile lipoid bodies were demonstrated under polarized light.

Sections of the leg veins revealed thrombi in varying degrees of organization. None of the leg or renal veins showed any evidence of phlebitis.

Comment: Multiple venous thrombi occurred in the veins of the lower extremities and kidneys of this diabetic patient with congestive heart failure. Clinically, the differential diagnosis of the etiology of the nephrotic syndrome was between diabetic glomerulosclerosis and renal vein thrombosis. The solution was unresolved at necropsy, since both lesions were present. Discrete focal areas of interstitial fibrosis with tubular atrophy and hyalinized glomeruli were more typical of arteriosclerotic scarring than of the more diffuse interstitial fibrosis attributable to chronic renal vein thrombosis.

Case 6. The patient was a 32 year old white male whose illness had begun at the age of 17 with the onset of ulcerative colitis complicated by pyoderma. After four months of conservative therapy, increasing weight loss and a progressive bloody diarrhea necessitated an ileostomy, which was performed in April, 1933. The postoperative period was complicated by the development of osteomyelitis of the left clavicle and an ischiorectal abscess. In November, 1934, the patient was rehospitalized because of extensive ulcerations of both medial malleoli, perineal fistulae and increasing rectal strictures. Examination of the urine revealed 4 plus albuminuria, and the sediment showed occasional white blood cells, with many hyaline and granular casts. The blood urea nitrogen was 9.0 mg. %. The total serum protein was 5.6 gm. %, with a serum albumin of 2.5 and a globulin of 3.1 gm. %. The hemoglobin was 9.0 gm. The red blood cell count was 3,600,000. The white blood cell count was 14,000, with a normal differential. A Congo red test revealed 90% retention. The patient was diagnosed as having secondary amyloidosis, and remained in the hospital for six months, with gradual improvement. His condition was apparently

quiescent until July, 1948, when a recurrence of an ischiorectal abscess developed. He was treated with parenteral penicillin, with gradual subsidence of the abscess.

The patient was re-admitted on October 26, 1948, because of the development of a rectal mass which, on biopsy, proved to be adenocarcinoma.

Physical examination revealed a chronically ill young male. The double-barreled ileostomy was clean and functioned well. The blood pressure was 90/60 mm. of Hg in each arm. Well healed scars were noted over both ankles. The heart and lungs were negative. The liver edge was palpable three fingerbreadths below the right costal margin. The spleen edge was barely palpable. Rectal examination revealed a necrotic mass. Two plus pitting edema was noted over both ankle regions. There was no evidence of pleural effusion or ascites. Sigmoidoscopy revealed that the rectal mass extended superiorly for a distance of 10 cm.

The blood urea nitrogen and serum creatinine were 33 and 2.5 mg. %, respectively. The total cholesterol and cholesterol esters were 422 and 309 mg. %, respectively. Urinalysis revealed a persistent 4 plus albuminuria. The urinary sediment revealed hyaline and granular casts. No doubly refractile fat or microscopic hematuria was observed. The hemoglobin was 9.0 gm., with a red blood cell count of 3,500,000. The white blood cell count was 7,500, with a normal differential count. The total serum protein was 3.9 gm. %, with an albumin of 2.0 and a globulin of 1.9 gm. %.

The patient was considered inoperable and was treated with radiotherapy. He became increasingly anorexic. The blood urea nitrogen increased to 115 mg. % terminally, with a serum creatinine of 4.5 mg. %. He became increasingly azotemic and died on January 4, 1949.

Necropsy: Final Anatomic Diagnosis: Chronic ulcerative colitis involving the entire large bowel; ileostomy; scars of healed ulcers of skin; adenocarcinoma of rectum with extension to perianal tissue and metastases to liver; amyloidosis of liver, spleen, kidneys, adrenal glands, and islets of Langerhans; organized and partially calcified thrombi in both main renal veins; chronic pyelonephritis; acute phlegmonous jejunitis.

The right kidney weighed 300 gm. and measured 12 by 6 by 3 cm. The left kidney weighed 280 gm. and measured 11 by 6 by 6 cm.

Both main renal veins were occluded by largely calcified thrombi which extended from the renal vein ostia into the venous radicles in the peripelvic fat and the renal substance.

The surfaces of both kidneys were smooth, and the organs were of increased consistency. The cut surface was discolored yellow and the cortices were widened.

The main renal veins and venous radicles exhibited a similar histologic pattern. The thrombi were completely organized by a dense fibrous tissue exhibiting extensive calcification. Tortuous endothelial-lined channels of recanalization were prominent in the peripheral portions of the thrombi. The venous walls exhibited fibrosis of the adventitia, but there was no cellular exudate.

The kidneys were severely involved by amyloidosis. Collecting and distal convoluted tubules exhibited distention by protein-rich casts. Tubular atrophy was marked, particularly of the proximal convoluted tubules. Scattered tubules were filled with an exudate of polymorphonuclear leukocytes. Sudanophilic fats and doubly refractile lipoid bodies were demonstrated in the epithelium of the proximal convoluted tubules.

Comment: Occlusive organized and calcified thrombi in the renal veins were associated with secondary renal amyloidosis. The extensive mineralization of the thrombi reflected the long duration of the process. In the presence of severe secondary renal amyloidosis, it is apparent that an evalua-

TABLE 1

Clinical Features

Patient	Age	Sex	Previous Illness; Clinical Findings	Known Duration of Nephrotic Syndrome	Edema	Intravenous Pyelogram	Hemoglobin gm./100 c.c.	Total Serum Cholesterol mg./100 c.c.
Case 1	39	F	Rheumatic heart disease, age 29; acute heart failure, pulmonary infarct, age 37; normal hemodynamics; right pleural effusion	6 mos.	Marked peripheral edema	Normal 2 mos. before death	13.0	400–900
Case 2	45	M	Right lumbar pain 6 yrs. and again 2½ yrs. prior to death; hypertension 1½ yrs. prior to death, 170/110; right pleural effusion; abdominal collateral venous circulation; severe bleeding internal hemorrhoids requiring transfusions; no cardiac failure	15 mos.	Marked leg and sacral edema, almost disappearing on mercurial therapy	Normal 27 mos. before death	11.8–12.8	548
Case 3	56	F	Carcinoma of the breast; bilateral pleural effusion; bilateral pathologic fractures of femurs	8 days	Massive edema of lower extremities	—	9.5	—
Case 4	70	F	Diabetic for 3 yrs.; arteriosclerotic heart disease 1 yr. before admission; bilateral pleural effusion; marked arteriosclerotic changes in fundi; no diabetic retinopathy	2 mos.	Marked edema of lower extremities	—	10.0	256–321
Case 5	72	M	Gangrene of both lower extremities and bilateral midleg amputations; diabetic	4–6 mos.	Marked edema of lower half of trunk and lower extremities	Nonvisualization	10.5	430
Case 6	32	M	Ulcerative colitis for 15 yrs.; ileostomy for 15 yrs.; extensive skin ulcerations; adenocarcinoma of rectum	Unknown	2+ pitting edema of ankles	—	9.0	422

Patient	Age	Sex	Serum Proteins gm./100 c.c.	Blood Urea Nitrogen mg./100 c.c.	Congo Red Test % retention	Urea Clearance % of normal	Urine			Complicating Renal Diseases
							Protein	Specific Gravity	Sediment	
Case 1	39	F	A. 2.2 G. 3.0	12.0	60	30	10–12 gm./24 hrs.	1.024	Occasional RBC and WBC; doubly refractile bodies not found on two examinations	None
Case 2	45	M	A. 1.7 G. 2.8	14.0	—	—	18–24 gm./24 hrs.	1.018–1.022	Occasional WBC, no RBC; numerous doubly refractile bodies found	None
Case 3	56	F	A. 3.7 G. 2.9	18.0–60.0	—	—	++++	1.010	Many fresh WBC, no RBC or casts; no study for doubly refractile bodies	None
Case 4	70	F	A. 3.3 G. 2.7	25.0–65.0	—	57 and 52	4.5–8.0 gm./24 hrs.	1.010–1.014	Occasional WBC, hyaline and granular casts; doubly refractile bodies found	Arterial and arteriolar nephrosclerosis
Case 5	72	M	A. 2.8 G. 1.8	67.0	—	—	++++	1.018	Numerous WBC; no doubly refractile bodies found on two examinations	Diabetic glomerulosclerosis
Case 6	32	M	A. 2.0 G. 1.9	9.0–115.0	90	—	++++	—	Hyaline and granular casts; no study for doubly refractile bodies	Amyloidosis

tion of the relation of occlusion of the renal veins to the nephrotic syndrome clinically and to any referable lesions in the kidney is impossible.

Analysis of Clinical Material

The clinical findings and laboratory data are summarized in table 1.

Age: The age of the patients varied from 33 to 76 years. Two of these patients were in the fourth decade of life.

Sex: There was equal distribution of the sexes in this small series.

Blood Pressure: Two of the patients were hypertensive at the time of admission to the hospital. One patient was normotensive but had had a history of hypertension and showed evidence of an enlarged left ventricle on fluoroscopy. The remaining three patients had normal blood pressures, and there was no evidence from the past history or from clinical examination of preëxisting hypertension.

Congestive Heart Failure: Three of the patients had recurrent congestive heart failure known for from two to seven years. Two of these three patients had extensive coronary arteriosclerosis with myocardial infarction. Rheumatic heart disease was the underlying cause in the third patient with congestive heart failure. The remaining three patients had no history in the past to suggest cardiac decompensation, and venous pressure and circulation time studies at the time of admission to the hospital were within normal limits.

Edema: All of the six patients disclosed edema at some time in the course of their illness. Five patients presented edema terminally. In one patient (case 6), edema was not present terminally, but this patient was on rigid salt restriction and cachectic, with no evidence of associated congestive heart failure. The remaining five patients had extensive edema of the lower extremities which was soft and pitting in character. In only two patients was there an associated bilateral pleural effusion, and in one of these (case 3) diffuse pleural and pulmonary metastases probably accounted in part for the accumulation of pleural fluid. Pericardial effusion and ascites were not evident in any of the six patients. In three of the patients venous pressures were markedly elevated in spite of digitalization, salt restriction and frequent mercurial injections. In these three patients, proteinuria varied from 8 to 24 gm. per 24 hours. The question of local venous occlusion in the region of the iliac veins or lower inferior vena cava as a contributory factor in the production of peripheral edema could not be adequately evaluated, since differential venous pressures in the upper and lower extremities were not measured prior to death. However, autopsy findings indicated that in four of the patients there was either marked narrowing or occlusion of the inferior vena cava and/or the iliac veins and their radicles.

Renal Function: The blood urea nitrogen and serum creatinine were either normal or only slightly elevated during the entire course of the patients' history except terminally in two patients, who showed evidence of a

rising blood urea nitrogen to azotemic levels. This was associated with congestive heart failure in one patient, and with what appeared to be progression of primary renal disease in the other. Intravenous pyelography was performed in three patients. In two of the patients, intravenous pyelography demonstrated prompt bilateral excretion of dye, with good visualization and no abnormalities of either collecting system. Nonvisualization of the upper urinary tract occurred in a third patient (case 5), but the blood urea nitrogen at the time of the procedure was 67 mg. %.

Urinary Sediment: There was no evidence of microscopic hematuria in five of the six patients. Only an occasional white blood cell was observed. Hyaline and granular casts were noted in all patients. No hemoglobin or red blood cell casts were noted. Broad renal failure casts were not observed in any of the six patients. Doubly refractile fat bodies were noted in two of the six patients (cases 2 and 4). A repeated fruitless search was made for anisotropic fat on fresh fairly concentrated urine sediments in two other patients (cases 1 and 5). In the remaining two patients only random urine specimens were studied.

Proteinuria: All of the patients manifested 4 plus proteinuria. The proteinuria was quantitated in three patients and the values ranged from 8 to 24 gm. per 24 hours. No real correlation could be made between the extent of the edema and the magnitude of the proteinuria. This lack of correlation, may, however, be due to associated factors in these patients, such as the presence of cardiac decompensation, the extent of salt restriction, and the degree of malnutrition.

Total Serum Protein: These values ranged from 3.9 to 6.6 gm. %. The albumin-globulin ratio was either reduced or showed complete reversal with diminution of serum albumin and with relative increase of the serum globulin fraction. Paper electrophoresis was performed in one of these patients (case 1). This revealed a decrease in serum albumin, with an elevation of the alpha-2 and beta globulin values. The gamma globulin remained within normal limits.

Serum Cholesterol: Five of the six patients disclosed hypercholesteremia, with a range of 321 to 900 mg. %. The serum cholesterol was not determined in the sixth patient. Lipids, phospholipids and total lipids were not determined.

Diabetes: The fasting blood sugar was elevated in two (cases 4 and 5) of the six patients. Diabetes was further confirmed by the presence of impaired oral glucose tolerance curves. One of these patients (case 5) showed typical lesions of diabetic intercapillary glomerulosclerosis at autopsy.

Serum Glycoproteins: Serum glucosamine and total serum protein-bound carbohydrate were examined in two patients (cases 1 and 5) and found to be significantly elevated.

Congo Red Test: A Congo red test was performed in three of the six patients and was positive in the one patient with amyloidosis.

Anemia: The hemoglobin and red blood cell count were maintained at fairly good levels until terminally, when all of the patients disclosed a depression of the hemoglobin and red blood cell count. There was no evidence in any of the patients of a primary blood dyscrasia.

Analysis of Pathologic Findings

The pathologic findings are summarized in table 2.

In three of the six cases described independent diseases of the kidney were present, characterized by anatomic changes of a type which could obscure intrarenal alterations due to occlusive renal vein thrombosis. These were renal amyloidosis, diabetic glomerulosclerosis, and severe arterial and arteriolar nephrosclerosis in a diabetic patient. The nephrotic syndrome in the former two instances could be explained by the coexistent renal disease, without invoking the role of occlusion of the renal veins.

Three of the cases herein reported revealed renal vein thrombosis without other independent diseases of the kidney. In two of these (cases 1 and 2) there were anatomic changes within the kidneys attributable only to chronic renal vein thrombosis. In both of these cases there was interstitial fibrosis with tubular atrophy. Sudanophilic neutral fats and doubly refractile lipoid bodies were demonstrated in the proximal convoluted tubules in one of the two cases in whom suitable material was available for study. In the other case numerous doubly refractile cells and casts were found in the urinary sediment during life. Interstitial fibrosis with tubular atrophy constituted the pathologic changes which have previously been attributed by others to renal vein thrombosis in adults. In association with these changes, the tubular deposition of sudanophilic fats and doubly refractile lipoid bodies has been reported but once previously, by Gerber and Mendlowitz.[3]

Until recently, distinctive glomerular lesions have not been described. Pollak et al.[9] described a case followed during life by serial renal biopsies. With progression of the disease in this case, unmistakable thickening of the glomerular capillary basement membranes supervened. The two cases herein reported that manifested interstitial fibrosis and tubular atrophy also showed thickening of the capillary basement membranes. In one of these (case 1), the glomerular capillary basement membrane thickening was mild and confined to glomeruli within the zones of interstitial fibrosis. The other (case 2) disclosed diffuse interstitial fibrosis, and all of the glomeruli in representative sections of the kidneys showed distinct thickening of the glomerular capillary basement membranes. The magnitude of this alteration is of considerable interest because of all of our patients, the nephrotic syndrome attributable to bilateral renal vein thrombosis was of greatest duration in this case. Anatomically, this glomerular lesion is indistinguishable from the lesion of membranous glomerulonephritis of varied etiology.[11]

The remaining patient (case 3) with no complicating renal disease showed no definite intrarenal lesions other than a few droplets of sudano-

TABLE 2—Pathologic Features

Patient	Pathologic Diagnoses	Renal Vein Thrombi	
		Main Veins	Venous Radicles
Case 1	Healed rheumatic mitral, tricuspid and aortic valvulitis; hypertrophy and dilatation of left auricle and right ventricle; chronic passive congestion of lungs, liver and spleen; organizing thrombi in renal, left ovarian and right adrenal veins	Early organization without recanalization	Organization with minimal recanalization
Case 2	Coronary arteriosclerosis, healed infarct of left ventricle; organized thrombi in inferior vena cava, renal veins, common iliac veins, testicular and adrenal veins	Complete organization with recanalization	Complete organization with recanalization
Case 3	Anaplastic carcinoma of right breast with widespread lymph node, visceral and bone metastases; invasion of inferior vena cava and renal veins with occlusion of left renal vein and narrowing of inferior vena cava and right renal vein	Lt. vein occluded and rt. vein narrowed by carcinoma	Patent
Case 4	Calcific aortic stenosis, hypertrophy of left ventricle; coronary arteriosclerosis, myocardial scars, thrombus in anterior descending branch of left coronary artery, recent myocardial infarction; arteriolar nephrosclerosis; chronic passive congestion of lungs; thrombi in both renal and ovarian veins, left adrenal vein and inferior vena cava	Organization with some recanalization	Complete organization with advanced recanalization
Case 5	Arteriosclerosis of peripheral and coronary arteries, myocardial scars; thrombi in leg veins, wounds of midleg guillotine amputations for gangrene; thrombi in renal veins, pulmonary emboli; cirrhosis of liver	Early organization without recanalization	Early organization without recanalization
Case 6	Chronic ulcerative colitis involving entire large bowel; adenocarcinoma of rectum with metastases to liver; secondary amyloidosis of liver, spleen, kidneys, adrenals and pancreas; chronic pyelonephritis; thrombi in renal veins	Complete organization with calcification and some recanalization	Complete organization with calcification and advanced recanalization

Kidneys

Patient	Weight Gm.	Coincidental Renal Disease	Interstitial Tissue	Tubules	Degree of Tubular Deposition of		Glomerular Changes
					Neutral Fats	Doubly Refractile Lipoids	
Case 1	Rt. 120 Lt. 130	None	Large focal areas of fibrosis	Atrophic in areas of interstitial fibrosis	Marked	Moderate	Mild thickening of capillary basement membranes in areas of interstitial fibrosis
Case 2	Rt. 170 Lt. 180	None	Diffuse interstitial fibrosis	Atrophic	Marked	—*	Universal marked thickening of capillary basement membranes
Case 3	Not weighed Rt. 10.5×5.0×3.0 cm. Lt. 10.5×5.5×2.5 cm.	None	Unremarkable	Unremarkable	Minimal	Minimal	None
Case 4	Rt. 110 Lt. 110	Arterial and arteriolar nephrosclerosis	Widespread focal fibrosis due to vascular disease	Widespread focal atrophy due to vascular disease	Marked	Moderate	Numerous hyalinized glomeruli due to arterial and arteriolar nephrosclerosis
Case 5	Not weighed Rt. 13×7×3 cm. Lt. 13×7×3 cm.	Diabetic glomerulosclerosis; arterial nephrosclerosis	Focal fibrosis due to vascular disease	Focal atrophy due to vascular disease	Moderate	Minimal	Occasional lesions of diabetic glomerulosclerosis
Case 6	Rt. 300 Lt. 280	Amyloidosis; chronic pyelonephritis	Amyloid depositions	Amyloid; casts	Marked	Moderate	Universal deposition of amyloid

* Suitable material not available for examination. Numerous doubly refractile lipoid bodies seen in urinary sediment during life.

philic fat and an occasional doubly refractile lipoid body in the tubular epithelium. The nephrotic syndrome in this patient developed during the last week of life.

It would seem that the short duration of the altered renal hemodynamics could account for the lack of anatomic changes. It must be noted, however, that a slowly progressive occlusive process involving the renal veins might permit an adequate collateral venous circulation to develop and so minimize the effects of occlusion of the main renal veins. That the development of an efficient collateral circulation may prevent or reverse the appearance of a nephrotic syndrome due to renal vein occlusion has been demonstrated experimentally in dogs by Rowntree et al.[12] This experiment has its counterpart in man in cases of chronic renal vein thrombosis where a nephrotic syndrome does not occur. Such instances have been reported by Harrison et al.[7] The inconstancy of renal parenchymal changes and of the nephrotic syndrome clinically in cases of chronic renal vein thrombosis suggests that there are definite gradations in the clinicopathologic picture. There is reason to believe that this depends on variable factors, which include the rapidity of the occlusive process, the adequacy of the collateral circulation, and the duration of life after occlusion has occurred.

Five of our cases showed variable degrees of organization and recanalization of the thrombi. In the sixth (case 3) the renal veins were compressed and invaded by carcinoma. The factors which determine the formation of thrombi in the renal veins are poorly understood. In the case of Schulman et al.,[4] the thrombi in the main renal veins were fresher than those demonstrated in smaller venous radicles. The implication was that the thrombi originated in the smaller venous branches, with forward propagation into the main renal veins. In two of our patients (cases 1 and 4) there was a similar difference between the extent of organization of the thrombi in the main renal veins and that in the intrarenal venous radicles. In two others (cases 2 and 6) the thrombi were completely organized and recanalized, both in the main renal veins and in the venous radicles. Of note was the extensive calcification of the organized thrombi in one (case 6) of these two cases.

The observation of differences in the age of the thrombi in the smaller venous radicles might suggest that the thrombi which occurred first within the kidney propagated into the main renal veins. However, this apparent age difference can as easily be correlated with the greater bulk of thrombosed blood undergoing organization in the main renal veins as compared to that in the smaller venous radicles. This explanation is supported in part by one (case 5) of our cases, who showed recent thrombosis with comparable degrees of early organization in both the main renal veins and venous radicles.

Pathogenesis

An analysis of our cases as well as of previously reported cases indicates that a fully developed nephrotic syndrome may develop in adult patients with

bilateral renal vein thrombosis. As with all cases of nephrosis, we can only conjecture as to the pathogenesis.

Allen [11] suggested that the extensive proteinuria was probably the primary incident, and that the basis for this was the increased pressure within the glomerular capillaries secondary to bilateral renal vein thrombosis. He also indicated that the alteration of the glomerular basement membranes in diverse renal diseases associated with a nephrotic syndrome such as diabetic glomerulosclerosis, renal amyloidosis, membranous glomerulonephritis, and eclampsia is responsible for the extensive proteinuria leading to a nephrotic syndrome. In two of our patients (cases 1 and 2), thickening of the glomerular capillary basement membrane indistinguishable from a membranous glomerulonephritis has been noted. It is not known whether this lesion is due to prolonged glomerular congestion or whether it is secondarily the result of prolonged proteinuria. The concept that glomerular basement membrane thickening occurs only after prolonged renal vein obstruction is supported by its maximal development in one of our cases, that of longest duration. Further support is gained from a recent study [9] in which serial renal biopsies in such a patient disclosed progressive thickening of the glomerular capillary basement membranes. The temporal factor may be modified by the adequacy of the collateral venous drainage.

Another important consideration in the pathogenesis of proteinuria and the nephrotic syndrome is the role of tubular atrophy and interstitial fibrosis. It is conceivable that this lesion may impair reabsorption of protein filtered by the glomerulus in normal or excessive quantities. This mechanism may be of importance equal to or greater than increased glomerular permeability.

Aside from anatomic considerations, other factors to be considered are the alterations in renal hemodynamics produced by obstruction of renal venous flow, and its effect on proteinuria as well as on electrolyte excretion.

Experimentally, Blake et al.[13] found that acute unilateral elevation of renal vein pressures resulted in a significant decrease of sodium and water excretion from the affected kidney, unassociated with alterations of renal hemodynamics. Selkurt et al.[14] also noted a depression of sodium and water excretion under similar conditions. However, a decreased renal blood flow and glomerular filtration rate was also demonstrated, but of a magnitude insufficient to favor sodium retention. Using inflatable balloons, Farber and his associates [15] produced elevated pressures at various levels of the inferior vena cava in human beings. Depression of salt and water excretion followed, whether the balloon was placed above or below the renal veins. Effects on renal hemodynamics could not be correlated with the degree of depression of salt and water excretion.

Prolonged elevations in renal venous pressure more comparable to those following chronic renal vein thrombosis have also been produced experimentally. Significant depression of salt and water excretion was produced by the methods of pericardial effusion [16] and ligation of the inferior vena cava

above the hepatic veins.[17] However, electrolyte excretion was unaffected by prolonged ligation of the inferior vena cava just above the renal veins.[18] It should be noted that an initial depression of renal blood flow, glomerular filtration rate and salt excretion was observed with return to normal levels after one week. This may reflect the development of an adequate collateral circulation.

Sirota and Nabatoff [19] compared individually the function of the right and left kidneys in a patient with unilateral renal vein hypertension secondary to splenorenal vein anastomosis. Prior to salt loading, there was a significant depression of the excretion of sodium, chloride and water by the kidney with elevated venous pressure. This was correlated with a reduced glomerular filtration rate. Under a salt load, the degree of depression of salt and water excretion by the affected kidney was greater than could be explained by the observed depression of glomerular filtration. A specific tubular effect of the venous congestion was postulated to account for the increased salt and water reabsorption during salt loading.

The precise mechanisms responsible for the nephrotic syndrome in adult patients with chronic renal vein thrombosis cannot be accurately defined. The importance of anatomic features, proteinuria and changes in electrolyte excretion, among other factors, is yet to be elucidated, as in other diseases of the kidney associated with a nephrotic syndrome.

The diagnosis of chronic renal vein thrombosis should be suspected in a patient with the nephrotic syndrome in whom the usual known causes can be excluded. Venography [7] and renal biopsy may be valuable aids in differential diagnosis.

Summary and Conclusions

1. A clinicopathologic study of six adult patients with chronic renal vein thrombosis has been presented.

2. Although all of the cases manifested a nephrotic syndrome, in only four of the cases was this attributable to bilateral renal vein occlusion per se. The other two cases were complicated by renal diseases which could have been associated independently with a nephrotic syndrome.

3. The inconstancy of the renal parenchymal changes was emphasized and discussed.

4. The fully developed renal parenchymal changes consist of interstitial fibrosis, tubular atrophy, thickening of the glomerular capillary basement membranes, and the deposition of sudanophilic fats and doubly refractile lipoid bodies in the tubular epithelium.

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SUMMARIO IN INTERLINGUA

Un studio clinicopathologic esseva facite in sex casos adulte de bilateral thrombosis de vena renal con le syndrome nephrotic. Le syndrome nephrotic esseva attribuibile a occlusion del venas renal in solmente quatro del casos. Un del remanente duo casos esseva complicate per amyloidosis renal secundari a chronic colitis ulcerative. Le altere exhibiva glomerulosclerosis diabetic a parte arteriosclerosis del vasos peripheric e multiple thrombos venose in le gambas. Tanto le un como etiam le altere de iste duo morbos renal pote associar se per se con un syndrome nephrotic. Occlusion del venas renal esseva associate con congestive insufficientia cardiac in duo casos, con compression e invasion del vena cave inferior e de ambe venas renal per carcinoma metastatic ab le pectore in un caso, e con nulle del usual causas predisponitori in le ultime caso.

Le patiente con le plus longe duration del syndrome nephrotic (15 menses) exhibiva diffuse fibrosis interstitial con atrophia tubular e uniforme spissification universal del membranas basal del glomerulos. Sudanophile grassias neutre esseva trovate in le epithelio tubular, e corpores lipoide a duple refractilitate esseva presente in le sedimento urinari durante le vita del patiente. Le patiente con le plus breve duration del syndrome nephrotic (octo dies) exhibiva nulle definite alterationes del parenchyma renal. Le tertie caso habeva un duration intermediari del syndrome nephrotic (sex menses), e etiam le grado del alterationes in le parenchyma renal esseva intermediari. Iste alterationes consisteva de extense zonas de fibrosis interstitial. Intra illos, il habeva atrophia tubular e leve grados de spissification del membranas basal del capillares glomerular. Grassias neutre e corpores lipoide a duple refractilitate esseva facilemente demonstrabile in le epithelio tubular. Le quarte caso esseva complicate per sever morbo de vasos renal, e il es possibile que isto celava le alterationes effectuate per le occlusion de venas renal.

Studios experimental con occlusion de vena renal in canes per Rowntree e Fitz indica que le disveloppamento de un efficace circulation collateral pote reverter le manifestation de un syndrome nephrotic. Il existe reportos de casos de bilateral thrombosis de vena renal sin le syndrome nephrotic. Le non-uniformitate del alterationes in le parenchyma renal e del presentia del syndrome nephrotic suggere que il existe gradationes in le tableau clinicopathologic. Plure rationes indica que illo depende de factores variabile, incluse le rapiditate del processo occlusori, le adequatia del circulation collateral, e le duration de vita post le occurrentia del occlusion.

Quanto al pathogenese, il non es possibile facer plus que conjecturar—hic como in omne casos de syndrome nephrotic. Proteinuria es possibilemente causate per le elevate pression glomerular o per le non-reabsorption de filtrate proteinas per le defective tubulos atrophic o per ambe iste factores. Experimentos con canes e studios in patientes human ha demonstrate que retention de sal e aqua occurre in consequentia del elevation del pression de vena renal. Le grado de iste retention excede lo que es explicabile per le observate relentation del filtration glomerular. Il es possibile que un specific mechanismo tubular resultante del congestion venose es responsabile pro le excessive retention de sal e aqua.

Venographia e biopsia renal pote esser de valor in le diagnose differential.

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CIRCULATORY ARREST IN PATIENTS WITH COMPLETE HEART BLOCK DURING ANESTHESIA AND SURGERY *

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INTRODUCTION

PATIENTS with heart disease generally fare well when operated on under present day anesthesia technics.[1, 2] The postoperative morbidity is higher in cardiacs,[3] but circulatory arrest during operation need not be anticipated. However, a recently suggested therapeutic measure, that of cholecystectomy for patients with heart block, Adams-Stokes attacks and symptomatic gallbladder disease,[4] has brought to operation a group of individuals in whom circulatory arrest is likely to occur. We have witnessed repeated episodes of circulatory arrest during operation in several patients with this combination of ailments. This has prompted us to review our prior experience with cases of this type. The present report is an analysis of the anesthetic and surgical factors leading to circulatory arrest during operation in patients with complete heart block.

We should like to emphasize that this is a rare type of circulatory arrest that should not be confused with the common cardiac arrest seen during anesthesia and surgery. In the former instance, circulatory arrest may be the result of asystole, ventricular tachycardia or ventricular fibrillation.[23] The treatment of these differs from that of the usual arrest, wherein immediate thoracotomy and manual cardiac systole may be indicated. A further reason for reporting this series of cases is that Zoll [5] and Bellet [6] have recently introduced new technics for the treatment of Adams-Stokes attacks and heart block which may be applicable during anesthesia.

CLINICAL MATERIAL

The files of the Peter Bent Brigham Hospital contained the records of 37 patients with complete heart block on whom operations had been performed. Anesthesia data were not available in six early cases, and in four operations had antedated heart block; in six, heart block was transient at the time of myocardial infarction or digitalis administration. Thus the records of 21 patients were available for study. An additional case observed by

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one of us at another hospital has been included. The essential facts of these cases have been summarized in table 1. There were 15 men and seven women. This predominance of males over females in patients with heart block has been commented on in another paper from this clinic.[7] The ages of the patients ranged from 14 to 78. The underlying heart disease was usually coronary arteriosclerosis or coronary sclerosis and hypertension. Congestive heart failure had been treated in many, and a few had hyperactivity of the carotid sinus. Complete heart block was present in all at some time or other preceding operation. Electrocardiograms confirmed the diagnosis in all but two cases. Other conduction defects, such as right or left bundle branch block, were also present in many. Eleven of the individuals had suffered Adams-Stokes attacks prior to operation. In some the attacks were infrequent, in others they occurred many times in the course of a day. The attacks conformed to the usual patterns of dizziness, weakness, syncope or convulsions. Fifteen of the operations were major, with cholecystectomy accounting for seven of these. The high proportion of cholecystectomies is due to the fact that this procedure had been looked upon favorably as a treatment for intractable Adams-Stokes attacks in this clinic.[4] The other major operations comprised thyroidectomy, gastric and intestinal operations, abdominal and gynecologic procedures, and inguinal herniorrhaphy. Four patients underwent two operations. The anesthetics employed are listed in table 1. Diethyl ether predominated in the major-operation group. Local anesthetics given for nerve blocks, and spinal and caudal anesthesia predominated in the minor group. The anesthetics were given by several categories of anesthetists, including nurses, surgeons and anesthesiologists.

TABLE 1

Major Complications in Patients with Complete Heart Block

No.	Name	Age	Sex	Hospital Number	Operation	Anesthesia	Adams-Stokes Attacks	Major Complication
1	A. F.	48	M	8B582	Cholecystectomy	Avertin-ether	Yes	Respiratory arrest
2	C. S.	52	M	5B143	Cholecystectomy	N_2O-ether: local	Yes	Circulatory arrest
3	L. C.	54	F	G5154	Cholecystectomy	Ether	Yes	—
4	J. R.	54	M	9B104	Inguinal hernia	Local	Yes	—
5	S. W.	57	M	S47986	Hemorrhoidectomy	Local	Yes	—
6	M. D.	62	M	7A519	Thyroidectomy	N_2O-ether	Yes	Circulatory arrest
7	J. G.	64	F	K5590	Cholecystectomy	N_2O-succinylcholine	Yes	Circulatory arrest
8	J. C.	68	M	R649	Femoral vein ligation	Local	Yes	—
9	G. D.	70	M	5A905	Cholecystectomy	N_2O-ether	Yes	Circulatory arrest
10	P. S.	72	M	F1078	Amputations	N_2O-spinal	Yes	—
11	C. D.	78	F	R1667	Cholecystectomy	Avertin-ether	Yes	—
12	J. D.	14	M	45661	T & A	Ether	—	—
13	J. M.	26	M	S6224	Hernia	Local	—	—
14	M. J.	42	F	M1486	Hysterectomy	N_2O-ether	—	—
15	J. M.	47	F	75395	Cholecystectomy	Ether	—	—
16	R. T.	52	F	101811*	Hemorrhoidectomy	Caudal	—	Circulatory arrest
17	E. S.	54	M	S66238	Amputation toes	Spinal	—	—
18	P. L.	55	F	3J591	Ovarian cystectomy	N_2O-ether	—	—
19	H. N.	55	M	49395	Gastrectomy	Avertin-ether	—	—
20	R. A.	60	M	7091	Carbuncle neck	Thiopental	—	—
21	R. M.	61	M	S43128	Thyroidectomy	Local	—	—
22	C. M.	71	M	18828	Resection rectum	Spinal	—	—

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It is a striking fact that in six patients, or 27% of the entire group, major difficulties consisting of episodes of respiratory and circulatory arrest occurred during the course of anesthesia or operation. Summaries of these cases follow.

Case Reports

Case 1. A 48 year old married factory foreman had had Adams-Stokes attacks and angina pectoris for seven years, during which time he had known complete heart block. For two years he had had infrequent attacks of burning epigastric pain unrelated to meals. One month prior to entry he experienced a severe episode of nausea and vomiting and right upper abdominal pain radiating to the back. At this time he also had a pronounced syncopal attack. There was no history of rheumatic fever, myocardial infarction, diphtheria or hypertension. Physical examination showed obesity, a pulse rate of 34, blood pressure of 115/40 mm. of Hg, slight enlargement of the heart, no murmurs, and a changing intensity of the first heart sound. Electrocardiograms revealed right bundle branch block, a ventricular rate of 29, and an auricular rate of 100. Roentgenographic examination showed a heart generally enlarged without calcification, and a poorly functioning gall-bladder.

On September 8, 1942, cholecystectomy was planned. He had been maintained on ephedrine for Adams-Stokes attacks, and received Pantopon, 15 mg., and atropine, 0.6 mg., hypodermically as preoperative medication. Induction of anesthesia was performed with rectal Avertin, followed by open-drop ether. The anesthetic record is incomplete. However, it was noted that *respiratory arrest took place twice during the operation and that a pulmotor was used for resuscitation.* Nothing was said about the circulation during respiratory arrest, but he recovered.

The patient was last seen in 1954, having had no further Adams-Stokes attacks. He had been working steadily and the physical examination and electrocardiograms were unchanged.

Comment: This operation was performed at a time when little attention was being paid to anesthesia, and the records were incomplete. Blood pressure was not recorded. Preoperative medication was not excessive for a man aged 48. It cannot be determined if the respiratory arrest was secondary to circulatory arrest. The fact that a pulmotor was required for resuscitation suggests that respiratory arrest was prolonged and severe, probably not due merely to overdosage with ether.

Case 9. A 70 year old male physician had had Adams-Stokes attacks for five years on the basis of presumed coronary artery disease without angina or known myocardial infarction. Right bundle branch block and transient complete auriculoventricular block were observed on the electrocardiogram. Syncopal attacks were noted to occur more often after meals consisting of fatty and fried foods. Two episodes of right upper quadrant pain and fever occurred within six weeks of entry, with increase of syncopal attacks to three to four a day. There was no history of rheumatic fever, diphtheria or hypertension. Physical examination revealed a well preserved elderly male, the heart rate regular at 80, a blood pressure of 134/86 mm. of Hg, grade 2 apical systolic and grade 1 aortic systolic murmurs, and no sign of congestive heart failure. Roentgenograms showed a heart normal in size and configuration, with calcification noted only in the arch of the aorta. Cholecystogram showed several calculi and poor function.

Cholecystectomy was planned for September 17, 1947. The patient had been receiving ephedrine for the Adams-Stokes attacks, and was given 10 mg. of morphine

and 0.6 mg. of atropine for preoperative medication. For some reason, after the start of anesthesia with nitrous oxide and ether, another 0.3 mg. of atropine was given. *As the abdomen was being prepared and an endotracheal tube passed, circulatory arrest occurred.* The skin color became ashen gray and respirations ceased. For one minute there seemed to be no cardiac activity, although an electrocardiogram was not available. Following 1.0 mg. intramuscularly and then 0.5 mg. of 1:1,000 epinephrine subcutaneously, evidence of circulation reappeared. The cholecystectomy then proceeded uneventfully. Recovery was uneventful. Adams-Stokes attacks disappeared. A year later the patient successfully withstood a cautery excision of a carbuncle of the neck under intravenous thiopental anesthesia. In 1949, Adams-Stokes attacks reappeared and he was treated with ephedrine and belladonna.

Comment: The preoperative medication may be considered excessive for a man of this age, though there is no record of preoperative hypotension or respiratory depression. It is interesting that a total of 0.9 mg. of atropine failed to protect against what might have been reflex stoppage of the heart at the time of endotracheal intubation. We do not know that a vagal reflex was responsible. There may have been anoxia at the time, a Valsalva effect consequent to breath holding and cough, or overdosage of anesthetic. There was no comment about these factors. Circulatory arrest, the nature of which is unknown, took place before operation had commenced and possible vagal reflexes from the surgical field could be induced. As in the first case, diethyl ether was the main anesthetic agent.

Case 6. A 62 year old white male developed frequent spells of unconsciousness following a slight head injury. He was forewarned each time by a pressure sensation over the precordium. The heart rate fell to approximately 20 per minute after each attack. Carotid sinus pressure had no effect on the heart rate between attacks. He had had a subtotal thyroidectomy in the past, and had been receiving 150 mg. of ephedrine daily to prevent Adams-Stokes attacks. There was no history of rheumatic fever, myocardial infarction or diphtheria. On physical examination the blood pressure was 160/100 mm. of Hg; the heart was not enlarged. Murmurs were not heard. A nodule was felt in the thyroid area. Electrocardiograms showed complete heart block and questionable left bundle branch block, with auricular rate, 120, and ventricular rate, 38. Occasionally normal sinus rhythm with right bundle branch block was in evidence.

On January 23, 1948, excision of the thyroid nodule was planned. The patient received Nembutal, 150 mg., morphine, 10 mg., and atropine, 0.3 mg., as preoperative medication. Electrocardiograms were taken continuously during induction of anesthesia with nitrous oxide and ether. After the start of anesthesia, normal sinus rhythm was replaced by complete heart block on the electrocardiogram. *Following endotracheal intubation there was a long period of asystole,* which responded favorably to 0.5 mg. of epinephrine given into the heart. Postoperatively pulmonary atelectasis, pneumonia and a left vocal cord paralysis developed. On the seventh day three Adams-Stokes attacks were observed. The patient was ultimately discharged from the hospital on digitalis and ammonium chloride. On subsequent hospital admissions Adams-Stokes attacks, diabetes and peripheral arteriosclerotic disease required continued treatment.

Comment: The preoperative dose of atropine was small in this case, though this probably had no bearing on subsequent events. This was the

first case in which an electrocardiogram was employed to monitor the circulation. It was extremely helpful. Diethyl ether again was the chief anesthetic agent. Complete heart block appeared after the start of anesthesia, and circulatory arrest took place at a time when vagal reflexes might have been initiated from the trachea. That reflexes from the trachea are not always vagal in type has been shown by the work of King et al.[8] The rôle of hypoxia, cough and myocardial depression cannot be ascertained. Reflexes from the operative field did not play a part in the development of circulatory arrest.

Case 2. A 52 year old physician had had severe diphtheria in childhood but was otherwise well except for mild indigestion and pylorospasm. One year prior to entry he first noted angina pectoris. There was no history of rheumatic fever, hypertension or known myocardial infarction. Two months before admission he had a syncopal attack diagnosed as Adams-Stokes disease. At the same time there was an increase in severity of indigestion. Intermittent right upper quadrant pain associated with nausea and vomiting was experienced. The syncopal attacks increased in number and severity and were thought to be related to the abdominal pain. The physical examination revealed a pulse rate of 42, blood pressure of 140/80 mm. of Hg, and no change in the first heart sound, though auricular sounds were heard. There was tenderness in the right upper quadrant. The electrocardiogram showed right bundle branch block intermittently with second degree block (2:1), and alternating with normal sinus rhythm. Roentgenograms of the heart were normal; no calcification was seen. Calculi were noted in the gall-bladder.

A first attempt at cholecystectomy was made on May 16, 1949, but was unsuccessful *due to four episodes of cardiac asystole prior to the surgical incision.* Operation had been started with an electrocardiogram running. Ten milligrams of morphine and 0.4 mg. of atropine had been given as preoperative medication, and nitrous oxide and ether were the agents used. Adrenalin was given twice via the intracardiac route and the heart pricked twice with a needle over the course of an hour. Asystole lasted for two minutes on one occasion. Finally operation was canceled.

Eight days later 100 mg. of Demerol were given for preoperative medication. Operation was begun with procaine infiltration of the skin, intercostal and field block. Asystole requiring intracardiac epinephrine again occurred. When intravenous Demerol failed to relieve painful stimuli from the operative area, ether anesthesia was begun. Repeated asystole occurred, with intracardiac epinephrine needed each time. The postoperative course was uneventful. Four years later the patient was working consistently and had had only one attack of syncope.

Comment: Continuous electrocardiography again proved helpful in making the diagnosis. Neither local nor general anesthesia was successful in preventing asystole, which responded repeatedly to cardiac stimulation from a needle, with and without the injection of epinephrine. It is probable that mere mechanical stimulation of the heart would have been enough. The frequency of asystole was far greater under anesthesia than had been true in the waking state. The episodes took place without reflex stimulation from the respiratory tract or operative field. Probably the anesthetics, procaine with its effect on the conduction mechanism of the heart, and ether, with a depressant effect on the myocardium, were responsible for asystole.

*Case 16.** A 52 year old woman had a history of sudden onset of fatigue and tightness in the chest on slight exertion six weeks prior to entry. Complete heart block, with a ventricular rate ranging between 40 and 48, was diagnosed by electrocardiography. There had been no Adams-Stokes attacks or history of diphtheria, rheumatic fever, angina or hypertension. She had been treated with Isuprel sublingually and ephedrine sulfate by mouth prior to admission to the hospital for excision of an anal fistula. Physical examination was negative except for slight ankle edema.

On July 8, 1953, the patient was given Seconal, 100 mg. by mouth, and morphine, 8 mg. subcutaneously, in preparation for a caudal anesthetic. The preoperative blood pressure was 110/70 mm. of Hg and the pulse 32. After a test injection of 5 ml. of 2% Cyclaine into the caudal canal, and a waiting period of five minutes, an additional 25 ml. of 2% Cyclaine were injected without recovery of blood on aspiration. *Within a minute there was a tonic convulsion, with opisthotonos and intense cyanosis.* When the patient was turned on her back the pulse could not be felt nor could the heart beat be heard. Convulsions continued as thoracotomy was performed. The heart was found in standstill, but resumed its contraction with manual systole. Intubation of the trachea was performed after intravenous thiopental terminated the convulsions. Intravenous norepinephrine and 0.6 mg. of atropine raised the blood pressure to 150/70 mm. of Hg and the pulse rate to 42. Two hours later the patient was completely responsive but with amnesia for the operative period. She recalled having failed to take her usual dose of Isuprel prior to operation.

Comment: A local anesthetic in the form of caudal anesthesia was chosen for this patient on the theory that general anesthesia for a simple rectal procedure was less safe. This patient had never had an Adams-Stokes syncopal attack. The convulsion and cardiac arrest might have been such an attack, or simply a reaction to the local anesthetic. The absorption of local anesthetics is known to be rapid from the caudal area. A high blood level of anesthetic resulting from the injection of 500 mg. of Cyclaine could easily have caused central stimulation leading to convulsions and cardiac arrest from depression of conductivity and contractility. Local anesthetics, because of their quinidine-like effect, are hazardous in the presence of heart block.[9]

Case 7. A 65 year old woman had had mild diabetes mellitus for 16 years and probable angina pectoris for three years without known myocardial infarction. After the onset of typical Adams-Stokes attacks, complete heart block was noted one year prior to admission. Syncope, at first occasional and mild, had recently become severe and averaged four a day. There was no history of rheumatic fever, diphtheria or hypertension. Intermittent right upper quadrant pain, nonradiating, had been noted for from one to two years. The physical examination revealed a pulse rate of 40 and blood pressure of 150/70 mm. of Hg. The first heart sound at the apex varied in intensity. A grade 2 systolic murmur at the aortic area, transmitted to the neck, and a split aortic second sound were heard over the precordium. Right upper quadrant abdominal tenderness was elicited. Electrocardiograms revealed complete heart block, and right bundle branch block with an auricular rate of 150 and ventricular rate ranging between 28 and 50. Roentgenograms showed the heart to be 20% enlarged to the right and left, and a cholecystogram demonstrated a single gall-stone, 5 cm. in

* We wish to thank those in the Anesthetic and Surgical Departments of the Hospital of the University of Pennsylvania who have given permission to report this case.

diameter. Ephedrine, adrenalin in oil, digitoxin, ammonium chloride and Isuprel had failed to suppress the Adams-Stokes attacks. On one occasion a Zoll cardiac pacemaker [10] had been applied, with equivocal results. Because of the suspected relation between attacks of right upper quadrant pain and Adams-Stokes attacks and angina, cholecystectomy was planned.

On July 6, 1954, the patient was given 1 mg. of epinephrine in oil intramuscularly, and Nembutal, 100 mg. by mouth. Anesthesia was begun, with continuous electrocardiographic observation and with a Zoll cardiac pacemaker in readiness. The preoperative pulse rate was 40. The anesthetics were nitrous oxide for analgesia and intravenous succinylcholine for muscular relaxation. Anesthesia and intubation of the trachea were uneventful. Thirty minutes after the start of operation the heart rate fell to 12, whereupon 1 mg. of epinephrine was given intravenously. The heart became irregular. Subsequently six episodes of asystole detected on the electrocardiogram were corrected by manual stimulation of the heart through the unopened diaphragm by the surgeon or by pounding of the precordium. Methoxamine was used to raise the blood pressure. Intracardiac epinephrine or cardiac manual systole was not necessary. Although the patient awoke immediately at the conclusion of operation, the heart once more had to be needled transthoracally for asystole. In the immediate postoperative period several episodes of asystole were treated by pounding the chest, intravenous injection of epinephrine, or the Zoll cardiac pacemaker. During the following week three mild syncopal attacks were noted. Later in the year recurrence of Adams-Stokes attacks seemed to occur with lapses in diabetic control.

Comment: This patient received adrenalin preoperatively, little preoperative medication, the advantages of continuous electrocardiographic observation of heart action, an artificial cardiac pacemaker in readiness, and anesthetic agents which are thought to have little effect on the myocardium. Yet asystole took place repeatedly. This occurred after the abdomen was open and cholecystectomy was in progress. Transdiaphragmatic manipulation of the heart and pounding of the precordium proved effective in correcting standstill. Later, needling the heart and the Zoll pacemaker proved effective.

Factors in Respiratory and Circulatory Arrest

1. *Medical Preparation of the Patient for Operation:* While patients with complete heart block usually receive no specific treatment except that for the underlying heart disease, those with Adams-Stokes attacks need treatment to prevent attacks and possible sudden death. Thirty-nine of 89 patients with complete heart block in Penton's series died suddenly.[7] A greater percentage of these deaths occurred among those with prior Adams-Stokes attacks. *Eleven of the patients in our series had had Adams-Stokes attacks, and five of the six persons who had respiratory and circulatory arrest during anesthesia and operation had had Adams-Stokes attacks.* The treatment of these five individuals before operation differed in no way from the treatment of those in the series at large. Thus atropine, ephedrine, epinephrine, Isuprel, thyroid, ammonium chloride and barium chloride had all been tried at one time or another in proportion to the severity and frequency of attacks. The opportunity to employ molar sodium lactate solutions, as suggested by

Bellet,[6] had not yet arisen. That none of these measures was certain in preventing attacks is indicated by the fact that a number of the patients were submitted to the risk of general anesthesia for cholecystectomy or thyroidectomy as therapeutic measures. The difficulty in evaluating agents and methods for the treatment of Adams-Stokes attacks is that the attacks are often infrequent and unpredictable in the time of appearance. The cause of the attacks is often unknown, and the means whereby heart action is restored are problematic.

In the treatment of heart block, atropine with a muscarinic blocking action mainly affects the sino-auricular and atrioventricular nodes, and only rarely affects conductivity in the ventricles. Epinephrine and norepinephrine and the sympathomimetic amines with positive inotropic and chromotropic effects will enhance myocardial contractility and accelerate the normal pacemakers. There is no reason to expect that an ectopic ventricular pacemaker will be equally affected. Digitalis, while necessary in the treatment of congestive heart failure and certain arrhythmias associated with heart block, carries the hazards of producing heart block in its own right. Despite the limitations of these pharmacologic agents, it is necessary to use them, since they are occasionally beneficial.

In the patient undergoing operation, drugs which have been helpful in the preoperative period should be given as part of the preoperative medication. The sympathomimetic amines may counteract the depressant effects of the general anesthetic agents on the myocardium. However, care must be taken to avoid the production of ventricular irritability, as has been observed with subsequent use of chloroform and cyclopropane.[11]

2. *Preoperative Medication and Anesthesia:*

a. *Preoperative medication.* Most of the patients in this series received standard preoperative medication, namely, an opiate and atropine or a derivative thereof. Some were given Avertin rectally for basal anesthesia, others a barbiturate derivative. It could not be determined if the choice or amount of preoperative medication had any bearing on the prevention or enhancement of circulatory complications arising during anesthesia. If apprehension were a factor in the appearance of Adams-Stokes attacks, fairly heavy sedation would be indicated. Reports of precipitation of attacks by emotional upsets and hyperventilation are on record. Conversely, it might be reasoned that the endogenous release of epinephrine and norepinephrine during anxiety or the adrenergic phase of stress might have a beneficial action on the myocardium in Adams-Stokes attacks. If morphine, Demerol or the other opiates are employed, there are associated pharmacologic actions which might contraindicate their use in the poor risk. It is a common property of all to produce arterial hypotension on a peripheral vascular basis, perhaps with some central effect.[12, 13] Hypotension is apt to occur with changes in position, particularly in the aged, where reflex vascular action is decreased. Heart block and Adams-Stokes attacks occur largely in the older age group,

often on the substratum of diffuse vascular disease.[7] With the exception of Demerol, the opiates evoke a parasympathomimetic response leading to increased vagal tone. None of these vascular effects is desirable in the patient with heart block.

Atropine is used routinely in anesthesia to inhibit salivary and bronchial secretions and to block reflex vagal action on the heart. The former goal is easily achieved with small amounts of medication, but large amounts are necessary to block vagal action. Those patients with circulatory arrest in this report received 0.3 to 0.6 mg. of atropine. Complete block of the vagus requires at least 1 to 2 mg. or more in man.[14] Whether these larger amounts can influence already existing heart block is problematic. On the other hand, larger amounts of atropine, through a sympathetic ganglionic blocking action, may produce arterial hypotension and interfere with the sympathetic influence on a ventricular pacemaker.[15]

b. *Anesthetic agents.* It is generally conceded that anesthetic safety lies more in good anesthetic management than in the choice of specific agents and technics.[16] Our report proves that anesthesia adds considerably to the risk of operation in patients with heart block. Three of the patients with anesthetic difficulty in this series had been given diethyl ether, one local anesthesia and ether, a fifth local anesthesia via the caudal route, and the sixth nitrous oxide and succinylcholine. It is a common property of the general anesthetics to depress myocardial contractility.[17] Though diethyl ether is purported to effect a reflex release of epinephrine that strengthens contractility,[18] the effect was not obvious or helpful in this series. Cyclopropane probably shares this effect, but might be interdicted because of the property of enhancing epinephrine-induced ventricular irritability. Its use in man has been avoided where epinephrine has been injected simultaneously. Nitrous oxide, with the least myocardial effect of all, is impotent as a general agent. Its excellent analgesic effect must be supplemented by intravenous barbiturates, and muscle relaxation is attained with curare or related drugs. This combination of agents employed in case 6 seemed to be safe until intraabdominal manipulation was started; at least, circulatory arrest appeared later than in the other cases.

If general anesthesia seems hazardous, local anesthesia might be safer. In most of the cases reported here, local anesthetics were employed with success. Infiltration, nerve block and spinal anesthesia were used, but largely for minor surgery. When major surgery was involved, as in case 4, local anesthesia was not effective in preventing circulatory arrest. Case 5 illustrates a failure with local anesthesia for a minor operation. The latter case, in which the circulatory reaction might have been an effect of the anesthetic absorbed into the blood stream, illustrates a pharmacologic property of the local anesthetics which is hazardous in heart block. The local anesthetics evince a quinidine-like effect on the heart and peripheral circulation. For this reason, intravenous procaine and the longer-acting derivative procaine

amide have been useful in the treatment of certain cardiac arrhythmias. The possible danger of impairing conductivity and contractility in heart block has been previously discussed.[9] If the local anesthetics are used, the addition of epinephrine to retard the absorption of the anesthetic might have an additional beneficial action in the myocardium. Epinephrine was not used with the local anesthetic in case 5.

c. *The surgical operation and peripheral reflexes.* Circulatory arrest took place during five major operations and one minor procedure. Four of the major cases involved cholecystectomy, a procedure suggested for the relief of Adams-Stokes attacks.[4] Arrest took place in four before surgical stimulation could be implicated, although subsequent periods of asystole arose during operative manipulation. In two instances (cases 2 and 3), cardiac asystole was noted at the time of endotracheal intubation. These observations emphasize the fact that, in addition to the adverse effects of anesthetics, reflex stimuli from various bodily areas may play a rôle. Vago-vagal reflexes have long been implicated in cardiac arrest during anesthesia.[19] Stimuli from the respiratory passages have been implicated, even though King et al. have shown that a sympathetic rather than a parasympathetic response is usually elicited.[13] There is also reason to believe that manipulation within the upper abdomen may have the same reflex effect on the heart. A possible reflex relationship between gall-bladder disease and angina pectoris or Adams-Stokes attacks has led to the performance of cholecystectomy for both these ailments. This clinical impression had been reinforced by experiments, in which stimulation in the area of the gall-bladder leads to cardiac abnormalities.[20] A similar train of events has been observed in man.[21, 22] Therefore, reflex stimulation from any bodily area, particularly the tracheobronchial passages and upper abdomen, may add to the possibility of circulatory arrest during anesthesia, especially in patients with heart disease.

Suggestions for the Management of the Patient with Heart Block Undergoing Anesthesia

Patients with heart block should be prepared for operation with the drugs which have been successful in preventing or alleviating Adams-Stokes attacks in the preoperative period. This may mean giving a slowly absorbed preparation of one of the sympathomimetic amines, one with a positive inotropic and chronotropic effect on the heart. A discussion of the drugs used to treat heart block and Adams-Stokes attacks appears in the papers of Zoll,[10] Penton,[7] Robbin [23] and Nathanson.[24] Epinephrine for intramuscular and intravenous use should be readied in the operating room. An intravenous infusion of isopropylarterenol (Isuprel), 2–6 μg/min. has proved to be sound preventive measure.

Molar sodium lactate, as suggested by Bellet,[6] should also be available. It is probable that the effectiveness of molar sodium lactate is due to the pro-

duction of alkalosis. In this connection it is interesting that Houle and co-workers at Minnesota have noticed a diminished cardiac and pressor response to epinephrine in the presence of acidosis.[27] The pressor response in patients with acidosis was increased with the injection of molar lactate or sodium bicarbonate. If respiratory acidosis during anesthesia is a factor in the development of the circulatory arrests in patients with heart block, better pulmonary ventilation and the injection of molar sodium lactate may enhance the response of the myocardium to endogenously released sympathomimetic amines.

Atropine in sufficient dosage to block the vagus should be given, bearing in mind that larger doses may produce hypotension by blocking ganglionic transmission in the sympathetic nervous system. To allay apprehension, small amounts of the barbiturates may be given, avoiding the opiates with their many adverse effects. The anesthetic agents chosen should be suitable for the contemplated surgical procedure and the agents with which the anesthetist is most familiar. For minor operations local anesthetics given by infiltration, block or spinal technics are better than is general anesthesia. However, local agents must be used in small amounts, with the addition of epinephrine to prevent rapid absorption and myocardial depressant effects.

Before induction of anesthesia, preparation should be made to monitor the electrocardiogram continuously. The value of this measure was seen in cases 2, 6 and 7, where the diagnosis of asystole was readily and promptly made. Asystole, ventricular tachycardia or fibrillation may precipitate circulatory standstill, and the treatment for each may differ. The electroencephalogram may be an equally important monitoring device in detecting cerebral hypoxia.[25] A final refinement could be the continuous recording of arterial blood pressure.

A great advance in the treatment of cardiac arrest has been made by Zoll and co-workers in their use of external electrical stimulation of the heart.[5] Although the pacemaker described by them has been unsuccessful in breaking through ventricular tachycardia and fibrillation, it has been highly successful in the treatment of Adams-Stokes attacks, reflex vagal standstill, drug-induced standstill and some cases of unexpected circulatory arrest during operation. Recently Zoll has devised a combined external defibrillator and pacemaker. To our knowledge the pacemaker had not been employed to treat Adams-Stokes attacks during anesthesia and operation. It was available for use in case 7, but simpler measures sufficed to institute effective ventricular activity. In the postoperative period, however, the device successfully reverted asystole. For the abovementioned reasons it is apparent that an artificial pacemaker of the Zoll type should be applied before the start of anesthesia, and maintained in readiness in the postoperative period. The device is hazardous in the presence of combustible anesthetics.

There are times during anesthesia for the patient with heart block when the possibilities of circulatory arrest seem greater, as when reflexes are

brought into play. This was seen in cases 6 and 9, when intubation of the trachea was performed. Coughing and breathholding leading to a Valsalva effect and the hypoxia common to both heighten the chances for circulatory arrest [26] when there is stimulation of the respiratory passages. Similar reflexes may be initiated by manipulation of structures in the upper abdomen.[21] In cases 1, 2 and 7, reflexes from the upper abdomen seemed to be involved in the repeated episodes of asystole or respiratory stoppage. Usually reflex activity is greater in the lighter planes of general anesthesia, but it would be equally hazardous to deepen anesthesia and risk direct myocardial depression with the general anesthetic agents.

When circulatory arrest occurs, any of a number of measures may be tried without immediate resort to thoracotomy and manual systole. Thoracotomy was performed only once in this series (case 16), and probably need not have been done. But the diagnosis of arrest must be made immediately and the measures instituted at once. Herein lies the value of the electrocardiogram and the electroencephalogram in making the diagnosis. The cardiac pacemaker can be triggered, a blow made to the precordium, the heart stimulated through the diaphragm if the abdomen is open, or the myocardium stimulated by a needle prick through the thorax. If there is further time, not exceeding a minute or two, epinephrine or molar sodium lactate may be given intravenously, but it is hard to conceive of their reaching the heart in the absence of circulation. *Only when these measures have failed should thoracotomy and manual systole be performed, though preparations should have been in the making all along.* When cardiac activity resumes, appropriate drugs to heighten myocardial conductivity and contractility and maintain an adequate systolic blood pressure must be given. A constant infusion of epinephrine, Isuprel or molar sodium lactate may be chosen. In the treatment of hypotension it will be best to avoid the pressor amines, which evoke a strong reflex carotid sinus response. Neo-synephrine, methoxamine and norepinephrine fall into this category.

Summary

It has been shown in patients with heart block, particularly those with prior Adams-Stokes attacks, that there is good reason to anticipate circulatory arrest during anesthesia and operation. Circulatory and respiratory arrest took place in six of 22 individuals with heart block undergoing operation. Fortunately there were no fatalities. Emergency thoracotomy was performed in one patient but this was probably unnecessary. The patients with heart block were in the older age groups, and mostly in the poor-risk category, because of the underlying heart disease. Those who developed circulatory arrest, with one exception, had had prior Adams-Stokes attacks, and all but one underwent a major operative procedure. Circulatory arrest probably was precipitated by a number of factors, but the

hazard of general anesthesia in some, of local anesthesia in another and of reflex initiation of arrest in several seemed fairly obvious. It has not been shown that the usual pharmacologic means for treatment of Adams-Stokes attacks were uniformly successful either before or during operation. The pharmacologic rôle of preanesthetic medications and of anesthetic agents in their possible effect on heart block has been discussed. It is not certain that any anesthetic technic is safe. Consequently a plan has been offered in the hope of minimizing the possibility of circulatory arrest and of treating arrest should it occur.

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SUMMARIO IN INTERLINGUA

Arresto cardiac sub anestheticos es usualmente inexpectate, excepte—forsan—in patientes subjicite a operationes cardiac. Patientes cardiac qui es operate pro altere conditiones presenta normalmente nulle difficultates in iste respecto. Tamen, in recente tempores nos ha vidite plure episodios de arresto cardiac in patientes con bloco de corde. Iste observation ha inducite nos a re-examinar previe experientias anesthetic con iste typo de morbo cardiac. Le constatation de un numero extraordinari de arrestos indica que arresto circulatori deberea esser considerate como un eventualitate non impossibile in iste gruppo de patientes e que le medios de prevention deberea esser investigate plus detaliatemente. Arresto circulatori es un melior termino que arresto cardiac, proque il ha essite monstrate que asystole, tachycardia ventricular, o fibrillation ventricular pote esser le evento primari.

Esseva studiate le dossiers de 22 patientes chirurgic con establite bloco cardiac complete. Le gruppo consisteva de patientes de etates plus avantiate, e sclerosis coronari o hypertension esseva usualmente le subjacente morbo cardiac. Dece-duo habeva habite attaccos de Adams-Stokes ante le operation. Dece-cinque del operationes esseva major, incluse septe cholecystectomias. Ethere diethylic esseva le principal agente in le operationes grave, e anesthesia local predominava in le interventiones minor. Il es un facto frappante que sex del 22 patientes habeva duo o plure episodios de arresto circulatori durante le stato anesthesiate e durante le operation. Felicemente nulle mortes occurreva, e thoracotomia de urgentia esseva effectuate in solmente un caso. In retrospecto on recognosce que le thoracotomia non esseva necessari. Le circumstantias accompaniante le arrestos circulatori es illuminatori.

Cinque del sex patientes con arresto habeva habite attaccos de Adams-Stokes que non respondeva al usual mesuras. Adrenalina, aminos sympathomimetic, atropina, thyroide, barium, e chloruro de ammonium non esseva efficace in prevenir le attaccos. Cinque del patientes esseva subjicite a operationes major, con cholecystectomia in quatro. Cholecystectomia ha essite proponite como mesura therapeutic pro alleviar morbo de Adams-Stokes quando un relation al vesica biliari es probabile. Atropina in doses usque a 0,6 mg como medication preoperatori non protegeva contra le arresto. Il es probabile, pro varie rationes, que plus grande doses haberea essite equalmente inefficace. Le effecto depressori de ethere super le myocardio esseva possibilemente responsabile pro le causation de arresto durante le induction in un caso. Similemente, le absorption rapide de un anesthetico local ab le sito de injection afficeva possibilemente le conduction cardiac in un secunde caso. In le altere casos, stoppage reflexe del corde es suggerite per le eventos precipitatori. Arresto circulatori sequeva

intubation endotracheic in duo casos; e le alteres esseva associate repetitemente con manipulation intra-abdominal. Omne le mentionate mechanismos ha resultate—individualmente o in combination—in arresto circulatori in patientes normal, sed le patiente con bloco cardiac es specialmente susceptibile.

Patientes con complete bloco cardiac deberea esser preparate al operation chirurgic per medio del drogas que es cognoscitemente capace a prevenir attaccos de Adams-Stokes ante le operation. On debe esser preparate a surveliar le electrocardiogramma continuemente. Adrenalina preste a esser injicite e un pacemaker cardiac externe del typo Zoll debe esser disponibile. Grande attention debe esser prestate a que doses excessive es evitate in caso de anesthesia general o de anesthesia local. Guardar se de arresto es specialmente urgente al tempore de stimulation reflexe. Thoracotomia non es necessari immediatemente post le occurrentia de arresto. In le casos hic reportate, action cardiac esseva reinstituite primarimente per medios mechanic. Batter le thorace, aguliar le myocardio, e stimular le corde via le aperte abdomine esseva mesuras efficace. In un caso un pacemaker cardiac externe esseva de valor.

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CLINICAL STAFF CONFERENCE

AGAMMAGLOBULINEMIA: CLINICAL STAFF CONFERENCE AT THE NATIONAL INSTITUTES OF HEALTH *

Participants: CHRISTOPHER M. MARTIN, M.D., EUGENE BRONSTEIN, M.D., and SHELDON DRAY, M.D., *Bethesda, Maryland*

CASE REPORT †

A 63 year old secretary was admitted to the Clinical Center on July 20, 1954, with a chief complaint of "low resistance."

Eight years previously, after having been well for 15 years, she had begun to have frequent upper respiratory infections, ulcers of the tongue and buccal mucosa, right costovertebral angle tenderness and "pleurisy." During the following year, at the age of 56, she contracted a fungus infection of the fingernails and recurrent sinusitis, tonsillitis and cervical adenitis. Blood studies by her physician revealed the hemoglobin to be 13.0 gm., and the total protein 6.5 gm. per 100 ml., with an albumin-globulin ratio of 3.6:2.9 (Howe method). She weighed 145 pounds.

Later that year a mass in the thymic area of the mediastinum was discovered and was treated with x-ray therapy. Because the mass shrank markedly, a retrospective diagnosis of lymphoma was made. Eight months later, at the age of 57, an "inflammatory process" in the head of the left humerus regressed under x-ray therapy.

Between the ages of 56 and 63 there were 15 to 20 attacks of febrile "grippe," 10 to 15 episodes of bronchitis, 12 to 14 pneumonias and bronchopneumonias, herpes zoster, skin nodules, mouth ulcers, recurrent oral, ungual and vaginal moniliasis, a chronic productive cough and repeated episodes of pyuria. At the age of 61 the weight was 114, and the hemoglobin was 11.4 gm. per 100 ml. Because of obstructive jaundice at the age of 62, an exploratory laparotomy was performed at another hospital. An enlarged liver and spleen were the only abnormalities noted; a specific diagnosis was not made, and the patient spontaneously recovered. During the year before admission she had diverticulitis, recurrent febrile diarrhea and several episodes of pneumonia, and ankle edema began to develop.

Before the present illness she had had a single episode each of mumps, rubeola and pertussis in childhood; typhoid fever at 13 years, scarlet fever at 16 years, quinsy with otitis media at 32 years, and jaundice of undetermined type at 40 years of age. She denied any allergies. The family and social histories were noncontributory.

Physical examination revealed a thin, pale, asthenic woman with a productive cough. Blood pressure was 110/76 mm. of Hg. There were tender erythematous papules scattered over the buccal mucosa, normal numbers of palpable lymph nodes, percussion tenderness over the maxillary and frontal sinuses, crepitant râles at both

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Requests for reprints should be addressed to Joseph J. Bunim, M.D., National Institutes of Health, Bethesda 14, Maryland.

† Case presentation by Dr. Martin and Dr. Bronstein. Reproduced in part by permission of the *New England Journal of Medicine.*

bases, a grade 3 apical systolic murmur, right costovertebral angle tenderness, enlargement of the liver and spleen to 5 cm. below the costal margins, and a vaginal discharge.

Examination of the blood disclosed a moderate normocytic, normochromic anemia, presumably hemolytic (hematocrit of 28.5 to 32.5% and reticulocytes of 2.0 to 5.4%), and a roughly cyclic neutropenia (white cell counts of 1,300 to 8,200, with 9 to 49% neutrophils); the platelets numbered 215,000; pyuria was demonstrated, and the maximal specific gravity of the urine was 1.018, but no proteinuria was observed. The blood chemical constituents (urea nitrogen, fasting glucose, sodium, potassium, chloride, carbon dioxide, calcium, phosphorus and alkaline phosphatase) were all within normal limits. Cephalin flocculation, thymol turbidity and zinc sulfate turbidity (Kunkel) were all 0. The total protein was 5.8 gm. per 100 ml., with an albumin-globulin ratio of 4.4:1.4 (26% sodium sulfate method).

Candida albicans was found in oral and vaginal secretions and paronychial scrapings; urine cultures were sterile. A Congo red test and several L.E. preparations were negative, as were skin tests against histoplasmin, coccidioidin and purified protein derivative. Bone marrow cultures failed to grow bacteria, fungi or mycobacteria. With the exception of three positive cultures during a single episode of bacteremia, 59 blood cultures over a seven-month interval were negative for aerobes and anaerobes.

Radiologic studies showed prominent bronchovascular markings, an ovoid mass 4.5 by 2.7 cm. in the anterior mediastinum (comparison with previous films revealed no change over the preceding three and one-half years), bone atrophy of the head of the left humerus, generalized osteoporosis and a filling defect of the right kidney.

The patient's blood was Type B and Rh positive, but there were no anti-A isoagglutinins in 1:1 dilution. Direct and indirect Coombs' tests were negative. Electrophoretic analysis of the serum of July 22, 1954, by the Rayleigh interferometric optical system technic, revealed an albumin of 3.44 gm. (normal, 4.5 ± 0.25 gm.), $alpha_1$-globulin of 0.45 gm., $alpha_2$-globulin of 0.61 gm., beta globulin of 1.21 gm., and gamma globulin of 0.11 gm. per 100 ml. (normal 1.1 ± 0.24).

Two bone marrow aspirates, taken before and after antigenic challenge, showed erythroid hyperplasia and no plasma cells. Review of the smears of a bone marrow aspiration performed 10 months before admission revealed no plasma cells. The paraffin blocks of a skin nodule on the thigh, a retroduodenal lymph node and a skin plaque on the left knee, removed elsewhere 17, 14 and eight months, respectively, before admission, were obtained, and sections stained with hematoxylin and eosin and periodic-acid-Schiff reagent. Reticulum cells, lymphocytes and well developed germinal centers were present in the lymph node, but on serial sections there were no demonstrable plasma cells, granulomas or fungi. Scalene lymph nodes were excised before and after antigenic challenge and stained with azure-eosin and methyl green-pyronine. Reticulum cells were present, but there were no germinal centers and only rare plasma cells.

On the nineteenth hospital day (nine days after retrograde pyelography) bacteremia and acute right-sided pyelonephritis due to *Escherichia coli* (communis) developed, followed by acute pericarditis with effusion four days later. From the twenty-seventh day to the thirty-seventh day a florid oral and vaginal moniliasis, numerous atrial arrhythmias, severe staphylococcal enterocolitis and congestive heart failure occurred in succession. With the aid of erythromycin, digitoxin, transfusions and supportive care, the patient slowly recovered.

In an attempt to prevent further infections, human gamma globulin was administered in doses of 0.1 gm. per kilogram of body weight every 14 days over a 57-day period.

There was virtually no change in the patient's condition. A second attack of acute pyelonephritis due to a species of paracolon bacillus, vaginitis and a severe upper respiratory infection that progressed to bronchopneumonia developed. The addition

of sulfadiazine in therapeutic dosage for the last 26 days of this 57-day period produced no striking change.

On the ninety-eighth day a single dose of 49.5 gm. of gamma globulin was administered as an isotonic clysis. Over the 79-day period after injection, while both digitalized and maintained at a serum sulfonamide level of 5 to 8 mg. per 100 ml., the patient underwent a remarkable improvement. Her only major infection was a bronchitis, which yielded to symptomatic therapy. The hematocrit steadily rose to a peak of 37.5%.

After a course of immunizations, a second large dose (46.0 gm.) of human gamma globulin was given by intramuscular and subcutaneous injections over a period of 16 days. Because of the appearance of sulfadiazine crystals in the urinary sediment, sulfadiazine was discontinued on the 182d day.

During the next 20 days, despite continued relatively high levels of serum gamma globulin (0.51 to 0.58 gm. per 100 ml.), the patient's condition steadily deteriorated. In that interval she contracted a syndrome of pharyngitis, leukopenia, atypical lymphocytosis and cervical lymphadenopathy (a questionable infectious) mononucleosis; an undifferentiated upper respiratory infection; sinusitis; and recurrent acute right pyelonephritis due to *E. coli* (communis), complicated, after antibiotic therapy, by a staphylococcal pharyngitis and diarrheal stools in which staphylococci predominated.

Over the following 50-day period, while once more receiving sulfadiazine sufficient to maintain serum levels of 5 to 7 mg. per 100 ml. and "maintenance doses" of gamma globulin, 5.0 gm. every eight days, the patient sustained a bronchitis from the 211th to the 214th day, and a mild upper respiratory infection from the 226th to the 232d.

After the 5.0 gm. gamma globulin dose on the 252d day, further injections were omitted for 41 days, and the serum gamma globulin level declined to 0.30 gm. per 100 ml. The patient was then placed on a new calculated "maintenance dosage" schedule of 5.0 gm. every 14 days. Over the 96-day period beginning on that day, while fully ambulatory at home, she sustained only a single mild upper respiratory infection, which occurred from the 267th to the 272d day.

Discussion

Dr. Christopher M. Martin: In summary, our patient is a 63 year old woman who until the age of 55 or so responded normally to infections. Over the next eight years, however, she developed increasingly severe and frequent bacterial infections, lost weight from 140 to 95 pounds, and acquired a progressive anemia.

Of particular interest is the evidence suggesting that the patient possessed significant amounts of gamma globulin at the onset of the disease—a normal albumin-globulin ratio.

May we see the patient's x-rays?

Dr. Eugene Bronstein: This series of chest films, from 1948 to the present, demonstrates originally a large anterior mediastinal mass, extending to both right and left of the midline, which decreased markedly in size under radiation therapy, and which has been stable ever since. The diagnostic possibilities are several—lymphoma, of course, thymoma or thymic enlargement, dermoid or teratoma, or radio-resistant lesions such as lipoma, substernal thyroid, or pericardial or bronchial cyst. Because of the later associated destructive process in the head of the left humerus—also radio-responsive—our original impression was reticulum cell sarcoma, which so often involves bone. The over-all stability of the

process, and the six-year period without recurrence, would tend to exclude lymphoma, however.

DR. MARTIN: The remainder of the protocol describes the numerous therapeutic twists and turns necessary to control this woman's repeated infections, and exemplifies the fact that in cases of agammaglobulinemia complicated by chronic infection, gamma globulin is by no means a panacea. It certainly is of value, but it takes second place to the far more potent antibiotics or chemotherapeutics, of which sulfadiazine and the tetracyclines have proved most valuable. The patient has therefore been maintained on relatively small doses of gamma globulin plus daily prophylactic chemotherapy over the last year and a half.

CLINICAL ASPECTS OF AGAMMAGLOBULINEMIA

The most extensive and fundamental studies of agammaglobulinemia have been done by Dr. Robert Good, of the University of Minnesota, and Dr. Charles Janeway and Dr. David Gitlin, of Harvard Medical School. We present today a summary of both their experience and that gained from our own five agammaglobulinemic patients.

The clinical syndrome consists of extreme susceptibility to infection, low to absent circulating gamma globulins and antibodies, immunologic unresponsiveness to antigenic challenge, and clinical improvement with replacement gamma globulin therapy.

The *physical signs* of the disease itself are really very few. First, there is generally diminished lymphoid tissue; in addition, where one expects an adenopathy of the regional lymph nodes in the presence of local infection, frequently there will be none. There is almost invariably some degree of hepatosplenomegaly, and in a number of cases there is a mediastinal mass—a hyperplastic thymus. The remaining (and predominant) physical signs are those resulting from severe, repeated bacterial infection.

Laboratory findings which suggest the diagnosis of agammaglobulinemia are, first, the virtual absence of gamma globulins and antibodies, including the natural isohemagglutinins. The latter are among the easiest antibodies to measure, since the appropriate technics are available in any blood bank.

Second, there are hematologic findings which indicate that the disease is not so specific as it would sound. As Good has shown, agammaglobulinemia is a generalized disease of the reticulum; his hematologic studies demonstrate clearly that there may be more than one differentiation defect in the reticuloendothelial system. A number of these patients may have, for example, almost complete absence of lymphocytes; indeed, in addition to their common plasma cell defect, virtually all of them eventually have further hematologic disturbances, the most common being a severe, recurrent neutropenia.

Third, there is usually diminished reactivity to antigens which detect delayed skin hypersensitivity. In the presence of demonstrable histoplasmosis, for example, these patients will tend to develop only weak skin reactions, if any. In addition, they have few allergies. On the other hand, a minority of patients with acquired agammaglobulinemia have a strict dichotomy of loss in their immune mechanism, being unable to make gamma globulins, but quite able to make fixed tissue or cellular antibody, the sort deemed responsible for delayed cutaneous hypersensitivity.

Fourth, a clinical hint which is sometimes of value in diagnosis is the fact that in the presence of known parenchymal liver disease, liver function tests of the flocculation type, which are partially dependent upon gamma globulin levels, may be negative or inordinately low.

Finally, there is a virtual absence of plasma cells in all tissues. In the most accessible tissue, the bone marrow, almost no plasma cells will be found after antigenic challenge.

The *major acute infections* which strike these people are principally bacterial. Pneumonia is the most common—chiefly pneumococcal; and meningitis is very severe, especially in children, related to the high incidence of otitis media. Hepatitis, especially serum hepatitis, is a major cause of death in these patients. Pyelonephritis is very common; their susceptibility almost defies the classic concept of Weiss and Mallory of the pathogenesis of pyelonephritis; they will develop it despite the absence of any obstructive phenomena in the genitourinary tract. Septic arthritis, with a concomitant bacteremia, is common. And, finally, a syndrome which very closely resembles acute infectious polyneuritis or Guillain-Barré syndrome, but which possesses none of the benign prognostic implications of that disease, is quite common. If these patients survive, their paralysis tends to be permanent.

The *chronic complications* of agammaglobulinemia are those that logically follow from the multiple acute bacterial infections: principally bronchiectasis, chronic pyelonephritis and pansinusitis. Because of the high incidence of bronchiectasis in this group, it is important to screen all patients with bronchiectasis for agammaglobulinemia.

Moniliasis of the mouth and nails is a most distressing chronic complication. Joint destruction occurs following septic arthritis, and brain damage and radiculoneuropathies subsequent to plastic exudates from repeated meningitides. Postnecrotic cirrhosis is common. Finally, hypersplenism is frequently encountered, aggravating these patients' already impaired hematologic differentiation mechanisms, and giving them some degree of hemolytic anemia, with or without splenic neutropenia and thrombocytopenia.

The *incidence* of the disease is very low. There are approximately 25 cases of the acquired type in the literature, and perhaps twice as many more that have not been reported. There are about 50 reported cases of the congenital disease; again, there are probably a good many more unreported.

The childhood form of the syndrome, although known as "congenital" agammaglobulinemia, is misnamed; it is a hereditary disease, a sex-linked recessive expressed only in boys, in the same manner as hemophilia, and with approximately the same frequency, about one out of 50,000 live births. The prevalence, of course, will probably increase in the next several years as antibiotics tend to save these patients from early death.

Regarding *etiology* of the acquired disease: one form is associated with clear-cut diseases of the reticuloendothelial system, and one idiopathic. Of the former group, the most prominent underlying disease is multiple myeloma, in which, although there is an excess of gamma-like globulin, there is a relative paucity of antibodies, and a functional agammaglobulinemia. As a result, the course of patients with multiple myeloma is usually marked by repeated septicemias. A few cases of agammaglobulinemia have also been described developing late in the

course of chronic lymphatic leukemia and, to a lesser extent, the lymphomas, principally lymphosarcoma.

The case of acquired disease presented this afternoon falls, we believe, into the idiopathic group. Several experimental phenomena have been cited as possible etiologies of the idiopathic disease. Among these is the phenomenon of *immunologic paralysis,* first described by Felton here at the National Institutes of Health some years ago. It consists of a degree of immunologic unresponsiveness, usually highly specific, induced in animals by the injection of massive amounts of pneumococcal polysaccharide. This phenomenon has since been shown not to be agammaglobulinemia, but an antigenic overloading of the animal's reticuloendothelial system, such that antibody, as soon as it is formed, is removed from the circulation by the intracellular polysaccharide not yet metabolized. It bears a certain relationship to the human disease, inasmuch as a number of these patients present as their first infection a severe type 1, 2 or 3 pneumococcal pneumonia. There, however, the analogy ends.

The phenomenon of *acquired tolerance,* recently described by Billingham and Medawar, may bear some relationship. Here, immunization of embryos with adult tissue cells permits that embryo, when it gives rise to an adult, to accept tissue homografts from the donor that originally supplied the cells. The phenomenon is highly specific, however, and thus far attempts to induct tolerance of antigens other than cells have been unsuccessful.

Reticuloendothelial blockade, of the sort produced by the injection of India ink into animals, has been implicated; yet the fact that phagocytic functions are intact in patients with agammaglobulinemia suggests that this is not the explanation.

Finally, agammaglobulinemia may fall in the category of *iso-immune diseases* akin to glomerulonephritis or rheumatic fever. There has been increasing evidence in a number of parallel directions that animals can be induced to make a wide variety of circulating and cellular antibodies against their own tissues (testicular, neural, renal, cardiac, etc.). The possibility exists that acquired agammaglobulinemia may result from manufacture of antibody against one's own antibody-producing system. Perhaps related to this hypothesis is the striking observation by Janeway and Gitlin in their group of agammaglobulinemic patients of symptoms and pathologic lesions closely simulating rheumatoid arthritis and dermatomyositis.

Studies in Agammaglobulinemia

Our primary research interest in these patients, over and above our efforts to keep them free of infection, has consisted of a comprehensive study of the normal immune mechanism, utilizing agammaglobulinemia as a background. Because of the relatively specific defect in antibody protein synthesis in agammaglobulinemia,* the disease is essentially analogous to the isolated defects in plasma protein synthesis in afibrinogenemia, hemophilia and other genetically-determined specific clotting defects, analbuminemia, and so on. These patients, therefore, offer an opportunity to set up experimentally defined conditions of gamma globulin metabolism which are susceptible to controlled measurement. In other

* Gitlin, Hitzig and Janeway have recently demonstrated the absence in agammaglobulinemic sera of at least two normal plasma proteins immunologically different from gamma globulins.[1]

words, agammaglobulinemia bears much the same relationship to the immune mechanism as does Addison's disease to adrenal function, and diabetes to carbohydrate metabolism. With this approach, we have attempted to gather fundamental data on the distribution, metabolism and synthesis of gamma globulins and antibodies.

Our first set of studies grew out of a therapeutic maneuver—loading each of our patients with a large dose of pooled human gamma globulin. After parenteral administration, the serum gamma globulin level was measured daily until the curve became linear, and then followed at intervals for from two and one-half to three months. We are indebted to Dr. Robert Gordon, of the National Heart Institute, for these measurements. The observed half-life of administered gamma globulin in our patient this afternoon was 36 days.

By extrapolating back to zero time the linear portion of the exponential curve of gamma globulin decline, one can determine the body fluid volume in which gamma globulin is diluted. Studies in four patients indicate that injected gamma globulin is dissolved in a fluid volume of approximately 10 to 12% of body weight; that is, slightly less than half of the injected gamma globulin remains intravascularly, while the rest is spread widely in interstitial fluid and in cells.

TABLE 1

Mean Half-lives of Passively Acquired Pooled Gamma Globulin and Antibodies in Four Agammaglobulinemic Patients

Antibody	Mean Half-life (Days)	Standard Error of Mean (Days)
Coxsackie A_{10} neutralizing antibody	21.7	1.9
Diphtheria antitoxin	31.7	3.4
Pooled gamma globulin	32.6	1.1
Poliomyelitis, type I, neutralizing antibody	32.8	1.0
Tetanus antitoxin	33.7	4.5
Typhoid-H agglutinin	35.2	1.5
Antistreptolysin O antibody	40.6	3.3
Adenovirus, type 2, neutralizing antibody	44.9	5.8

At the same time that we followed the declining serum gamma globulin levels, we measured the decline of individual antibodies derived from the administered gamma globulin; it turned out, surprisingly, that individual antibodies are degraded at quite different rates. The mean half-lives of seven common antibodies in four patients (table 1) ranged from 22 days (Coxsackie virus neutralizing antibody) to 45 days (adenovirus, type 2, virus neutralizing antibody), while the half-life of pooled gamma globulin was 32.6 days. At the same time, the data indicated that each species of antibody is destroyed at about the same rate in each patient.

In seeking a mechanism for this phenomenon, we have had the opportunity to conduct joint antibody fractionation studies with Dr. Herbert Sober and Dr. Elbert Peterson, of the National Cancer Institute. Preliminary data indicate that by ion-exchange chromatography of human gamma globulin it is possible to fractionate individual antibodies on the basis of subtle differences in physicochemical properties. The ion-exchange column arranges the antibodies in order, from those with the fastest electrophoretic mobility and the highest charge to those with the slowest electrophoretic mobility and the lowest charge. Further-

more, the antibodies emerge from the column not in random order, but in very much the same order in which the agammaglobulinemic patients degrade them: the first antibody to emerge in the fractions is Coxsackie, and the last, adenovirus.

Initial studies therefore permit the hypothesis that, in a closely related group of proteins of virtually identical molecular weight and composition, the rate of metabolism (or, perhaps, passage through cell membranes) may be closely correlated with the electrophoretic mobility of the molecule.

Passing now to studies on the synthesis of gamma globulin: we made use of the fundamental demonstration by Dr. Good that normal skin, when homotransplanted to a congenitally agammaglobulinemic child, would survive for many months; this is in contrast to the normal, in whom homotransplanted skin sloughs in a matter of from 10 to 14 days.

Good also achieved the corollary of this experiment, which was to endow an agammaglobulinemic patient, at least for a time, with a miniature reticuloendothelial system, through transplantation of a lymphoid tissue. We therefore chose this system as an experimental model for obtaining quantitative data on the rate of synthesis of gamma globulin by a human tissue.

In June, 1955, eight abdominal lymph nodes were excised from a normal, unsensitized donor, who was undergoing surgery for other reasons, and the nodes transplanted as tissue slices to the thighs of an agammaglobulinemic recipient, our patient this afternoon. Both recipient and donor were then challenged with typhoid vaccine. In response to antigenic challenge 7, 14 and 20 days after transplantation, the previously unresponsive recipient made typhoid H and O antibodies which then persisted for a long period. She had further responses to booster doses of vaccine on the 68th and 98th days. Declining responses to later antigenic challenges indicated that the death of the nodes occurred between the 150th and 160th days.

A biopsy of one of the nodes, 19 days after transplantation, showed cords and strands of lymphoid tissue, thoroughly penetrated with granulation tissue, undergoing a moderate plasmacytosis. Extracts of the biopsy were rich in typhoid H and O antibody. In contrast, biopsies of the recipient's scalene nodes, before and after transplantation, revealed structureless, quiescent lymphoid tissue, extracts of which contained no detectable antibody.

In order to estimate the rates at which the transplant synthesized antibody, it was necessary to derive by immunochemical procedures a constant relating units of typhoid agglutinin activity, measured by biologic assay, to micrograms of typhoid antibody nitrogen. It was found, for example, that one unit of the recipient's typhoid-O antibody activity is equivalent to 0.10 microgram of typhoid-O $beta_2$-globulin nitrogen/ml. By multiplying this constant times the daily increment in serum titer, the pool size of typhoid antibody, and the figure 6.2, which relates antibody nitrogen to antibody protein, and dividing through the whole expression by the weight of the transplanted tissue (845 mg.), we were able to estimate each day's rate of synthesis of gamma and $beta_2$-globulin by the transplant.

Typhoid-H gamma globulin was synthesized during the primary immune response at a maximal rate of approximately 6 mg. per gram of tissue per day. At the peak of the secondary response there was a rise in production to approximately 11 mg. per gram of tissue per day. As expected, the rates of synthesis of typhoid-O $beta_2$-globulin were lower, and peak rates were achieved more slowly.

In table 2 our own data are compared with the results of several studies in

animals, and with estimates derived from recent biosynthetic turnover data on protein synthesis in man. It can be seen that in response to a moderate challenge, and with no previous experience with the antigen, human lymphoid tissue can rapidly synthesize a highly specific product at rates which are quite comparable with those at which exocrine, endocrine and liver tissues turn out such unvarying products as enzymes, hormones and plasma proteins.

Future studies of agammaglobulinemia in this laboratory will probably consist of: (1) an investigation into the etiology of the disease, and (2) attempts to

TABLE 2

Measured Rates of Protein Synthesis by Various Human and Animal Tissues, and Rates Estimated from Recent Human Biosynthetic Turnover Data*

Tissue	Protein Synthesized	Conditions	Rate of Synthesis (mg./gm. wet weight tissue/day)
Human Tissues, in vivo			
Lymph Node (Transplant)	Typhoid-O Beta$_2$-Globulin	Peak, I° response Peak, II° response	3.6 10.5
	Typhoid-H Gamma Globulin	Peak, I° response Peak, II° response	6.0 11.0
R-E System	Gamma Globulins	Steady state	1.7–5.8
Liver	Total Plasma Protein	Steady state	7–15
	Albumin	Steady state	2.9–10
Animal Tissues, in vitro			
Liver (Rat)	Total Plasma Protein	Optimal perfusion conditions	15–18
Liver (Chicken)	Albumin	Optimal incubation conditions	2.5–3.0
Pancreas (Pigeon)	Amylase	Tissue slices depleted of zymogen	15–25
Anterior Pituitary (Rat)	Protein Hormones	Optimal incubation conditions	45–55

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dissect the various phases of the immune response, employing the fluorescent antibody technic developed by Dr. Albert Coons, of the Harvard Medical School.

DR. SHELDON DRAY: The experimental studies with agammaglobulinemic patients, as indicated by Dr. Martin, yield very useful information concerning the nature of gamma globulin and antibody metabolism in man. Although the total quantity of gamma globulins in serum can be determined readily, the interpretation of these values is somewhat limited because they represent the summation of values for a number of different gamma globulins.

As shown by Dr. Martin, the experimental studies are made more meaning-

ful by using the sensitive technics which are available for the analysis of specific components in the gamma globulin fraction. Well characterized antibodies are most suitable for study because of the high specificity and sensitivity of the known immunologic methods available for analysis. In addition, antigens can be used to stimulate specifically the production of their characteristic antibodies.

On the other hand, it should be recalled that the known antibodies represent only a small part of the total gamma globulins in normal serum. Antibodies seem to be generally indistinguishable from normal gamma globulins with respect to amino acid composition, solubility properties, electrokinetic properties and molecular weight. Even when injected into animals as antigens, the specificities of antibodies and normal gamma globulins are identical. Thus, antibodies may be distinguished from normal gamma globulins only by their capacity to combine with the specific antigens used for their production. However, it is conceivable that the normal gamma globulins are antibodies which have not been tested, or are antibodies not detectable by the known immunologic reactions. In this respect there is some evidence which indicates that antibody synthesis is related to gamma globulin synthesis. For example, gamma globulin is increased during immunization; in hypogammaglobulinemic patients, antibody formation is decreased.

On the other hand, evidence from studies on specific antibodies presented above seems to indicate that there are at least some differences in the metabolism of the various antibodies, and these results would suggest differences also in the other gamma globulin components. Nevertheless, the results from studies on antibody metabolism will undoubtedly contribute a great deal to the understanding of gamma globulin metabolism in general.

Although the immunologic methods of analysis for the components of gamma globulin are quite sensitive, their limitations should not be overlooked. A few examples will be mentioned.

The comparison of the quantities of various antibodies determined by such procedures as precipitin tests, complement fixation tests, hemagglutination tests, etc., which have different degrees of sensitivity and measure the quantity of antibody in different units, leads to difficulties. As shown above, it was necessary to derive a relationship between typhoid agglutinin activity measured by biologic assay and micrograms of typhoid antibody nitrogen. Ideally, it is preferable to select antibodies for study which can be measured directly in metric units. Unfortunately, the antigen-antibody systems available for such quantitative studies in man are restricted at present to only a few. A more general study of gamma globulin and antibody metabolism will require animal experimentation.

Even under the best of conditions, with pure soluble antigenic proteins yielding precipitating type antibodies, the results will require careful interpretation. The immunologic methods of analysis depend on the high degree of specificity of the antigen-antibody reaction. This specificity is based on a structural complementariness between the combining regions of antigen and antibody. The reaction is due to the accumulation of three types of relatively weak attractive forces (electronic, electrostatic and hydrogen-bond forming forces) existing over a large enough surface of the two molecules. Since a molecule of antigenic protein may contain more than one particular configuration of amino acids as an antigenic determinant, it follows that this molecule may elicit many different antibodies. Thus, some antibodies may form which have combining sites directed toward various single portions of the antigen, and some which are directed

against structural complexes involving adjacent portions of two antigenic determinant surfaces. This kind of heterogeneous response to a pure protein is particularly evident with conjugated proteins. The heterogeneity of antibodies is known to be a complicating feature of some antigen-antibody reactions.

Summario in Interlingua

Es presentate un caso de agammaglobulinemia acquirite. Le patiente esseva un femina de 63 annos de etate. Attention special es prestate a problemas de therapia prophylactic. Es discutite le characteristicas clinic e laboratorial del syndrome de agammaglobulinemia e etiam su incidentia, su typos, su complicationes principal, e le possibile etiologias.

Studios quantitative in patientes con agammaglobulinemia demonstra que individual anticorpores human es degradate a differente grados de intensitate, que homotransplantas de tessuto lymphoide es capace a superviver pro longe periodos in patientes agammaglobulinemic, e que in responsa a stimulos antigenic le human tessuto lymphoide es capace a synthetisar specific proteinas anticorpore a alte rapiditate. Le signification inherente de iste constatationes es discutite. Es offerite un evalutation critic del methodologias contemporanee pro le studio del mechanismos immunologic.

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CASE REPORTS

FATAL POLYCYTHEMIA FOLLOWING PERNICIOUS ANEMIA TREATED WITH VITAMIN B_{12} *

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Introduction

Since the introduction of specific therapy for pernicious anemia, persons with this disease have lived sufficiently long to develop other disorders of the hematopoietic system. A striking but distinctly unusual instance of this has been the development in such patients of polycythemia vera. Such cases would appear to be interesting in light of the frequent speculation concerning the etiology and pathogenesis of pernicious anemia and polycythemia rubra vera.

A review of the literature reveals several instances of polycythemia developing in association with liver therapy, and a few cases of typical polycythemia vera associated with or following treatment for classic addisonian pernicious anemia.[5, 12, 14, 15, 18, 20, 24, 32, 34] However, there are no reports of autopsied cases of such a polycythemia, and only one report of a patient who developed polycythemia vera after vitamin B_{12} therapy. The present report describes a case in which fatal polycythemia vera developed after treatment of pernicious anemia with vitamin B_{12}.

Case Report

A 58 year old white Hungarian male insurance salesman was admitted to City Hospital, Cleveland, Ohio, on November 3, 1950.

Past History: Six years previously he had had his first hospital admission to another hospital for herniorrhaphy, at which time a single hemoglobin determination of 84% was reported. Three and one-half years previously he had had his second hospital admission to that same hospital, with complaints of paleness, weakness, weight loss, and numb and freezing sensations in his feet. There was no history of alcoholism, diet deficiency or exposure to chemicals. Positive physical findings were limited to pallor and impaired vibratory and position sense of both feet and lower legs. He had an anemia (table 1) of 1.0 million red blood cells per cubic millimeter, 1% reticulocytes, 8,000 white blood cells per cubic millimeter, 72,000 platelets per cubic millimeter, achlorhydria following histamine, normal icterus index, and a megaloblastic bone marrow. With one transfusion and 15 units of liver extract intramuscularly daily, he showed a response of 12.4% reticulocytes on the tenth day of therapy, and a red blood cell count of 3.90 million per cubic millimeter on the fourteenth day. After discharge he was maintained by his physician on 20 to

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TABLE 1

Hematologic Data on a Patient with Pernicious Anemia, Who Developed Polycythemia

Date	Condition	Prior Therapy	Hemoglobin, gm.	Hematocrit, %	Red Blood Cells, millions	Reticulocytes, %	White Blood Cells, thousands	Neutrophils	Juveniles	Lymphocytes	Monocytes	Eosinophils	Basophils	Platelets	Comment
1944	Inguinal hernia	None	84%				23								Asymptomatic
1947	"Weak" Admission (2-28)	None	22%	7	1.0	1	8.0	89	0	9	1	1	0	72,000	Marrow—megaloblastic
	Discharge (3-14)	Liver 15 units q.d.; 500 c.c. transfusion	68%		3.9	6.5	26.5	83	8	5	2	2	0	200,000	Symptomatically improved
1950	"Weak" Admission (2-20)	30 units liver q. week	7.4		1.6	4	21.4	81	0	17	1	1	0	200,000	Marrow—consistent with P. A. in relapse
	Discharge (3-17)	15 mcg. B_{-12} q.d.; 1,000 c.c. transfusion	14.5	50		6		91	1	6	1	1	0		Marrow—normal Improved symptomatically
1950	"No symptoms" Office (9-9)	15–30 mcg. B_{-12} each month	14.0		4.8		40	85							No abnormal white cells Felt well
1950	"Coma" Admission (11-3)	None	23	79	8.7		75.0	94	0	4	1	1	0	"adequate"	
	(11-8)	I.V. fluids Phlebotomy 1,000 c.c.	17	52	7.7		61.0	99	0	1	0	0	0		

30 units of parenteral liver extract monthly, with complete remission of the anemia and all symptoms.

He did well until December, 1949, when he developed a progressive anemia despite injection of 30 units of liver extract weekly. He complained of dyspnea, palpitation, weakness, and a return of the neurologic symptoms. He was admitted for the third time to the same hospital in February, 1950, where he was found to have pallor, tachycardia, hepatomegaly, splenomegaly, positive Romberg's sign, and decreased position sense and deep tendon reflexes in both legs.

Examination of the blood (table 1) showed anemia and polymorphonuclear leukocytosis. Four per cent reticulocytes were reported at that time. Bone marrow studies showed 1.6% megaloblasts and 13.6% erythroblasts, with the added note by the pathologist that many of the erythroblasts may actually have been megaloblasts. No other blast forms were noted, and the impression was "consistent with pernicious anemia in relapse." Serologic test for syphilis, liver function tests, electrocardiogram, chest x-ray, gastrointestinal series and barium enema all were reported as normal.

Following two transfusions of 500 c.c. of whole blood and 15 μg of vitamin B_{12} daily the red count rose steadily, so that 25 days after beginning therapy the anemia was completely corrected; however, the leukocytosis persisted (table 1). The bone marrow was reported as active, with no megaloblasts, and completely within normal limits. The patient was symptomatically normal. The only reticulocyte count after beginning therapy was 6% on the tenth day of therapy.

Thereafter he received monthly injections of vitamin B_{12} from his physician and continued to feel well, with normal hemoglobin and red cell levels. In August, 1950, he received his last B_{12} injection. At that time the splenomegaly was still noted. On September 9, 1950, he was asymptomatic, and peripheral blood showed 4.9 million red blood cells per cubic millimeter, 14.5 gm. % hemoglobin, and 40,000 leukocytes per cubic millimeter, with 85% segmented neutrophils and "no abnormal cells." On October 17, 1950, he was asymptomatic but had a plethoric countenance. Shortly thereafter he complained of frequent headaches.

Fourth and Final Admission: On November 2, 1950, while walking on the street, the patient became dizzy and fell, sustaining a scalp laceration which was sutured at another hospital. The next day he was stuporous and was taken to City Hospital, Cleveland, Ohio, and admitted in a semicomatose state.

Physical examination on admission revealed temperature, 37.3° C.; pulse, 100; respirations, 18; blood pressure, 140/90 mm. of Hg. He was cyanotic and plethoric in appearance, but not dehydrated. There were ecchymoses over both knees and elbows, petechiae over the left arm below the site of the sphygmomanometer and in oral mucous membranes, and submucous hemorrhages in the nasal mucosa and tympanic membranes. No adenopathy was noted. No abnormalities were found in the heart or lungs, and peripheral pulses were all palpable. The liver and spleen were palpable 4 cm. below the costal margin. The eyegrounds revealed retinal venous engorgement but no papilledema or hemorrhage. Neurologic examination was negative except for paralysis of the lateral rectus muscle of the left eye.

The laboratory findings on admission revealed a marked polycythemia and leukocytosis, as indicated in table 1. The platelets were described as adequate in number on the blood film; the bleeding time was 1.25 minutes by the Duke method; the clotting time was 10 minutes, and the clot retraction was normal. The Rumpel-Leede test was strongly positive. The urinalysis showed $\pm$ albumin but was otherwise negative. The lumbar puncture revealed grossly bloody fluid under reduced pressure. Other laboratory findings showed blood urea nitrogen, 29 mg. per 100 c.c., fasting blood sugar, 99 mg. per 100 c.c.; total proteins, 7.4 gm. per 100 c.c.; albumin, 5.0 gm. per 100 c.c.; globulin, 2.4 gm. per 100 c.c.; carbon dioxide combining power, 49 vol. %; calcium, 9.3 mg. per 100 c.c. The serologic test for syphilis was negative.

The patient was maintained on parenteral fluids and tube feedings. His level of consciousness fluctuated during the next several days, and daily lumbar punctures were grossly bloody under normal or reduced pressures. Following phlebotomy of 1,000 c.c. on the fourth hospital day the red blood cell count was 7.7 million per cubic millimeter; leukocyte count, 52,000 per cubic millimeter. On the seventh day lumbar puncture contained 6,000 red cells per cubic millimeter. On the eighth day another phlebotomy of 500 c.c. was done. All during the first week vital signs were unchanged.

During the next week his temperature slowly rose. He was maintained on tube feedings and intravenous infusions, with 300,000 units of penicillin each day. Suddenly, on the morning of November 18, he slipped into a deep coma; his temperature rose to 41° C., pulse to 140 to 160, and blood pressure to 70/40 mm. of Hg. He died quietly that afternoon.

Autopsy Findings: Autopsy revealed, grossly, a white plethoric male with injected mucous membranes and multiple ecchymotic areas. All organs were congested and dark blue, and the brain appeared hyperemic. In addition, the brain showed multiple areas of hemorrhage and necrosis measuring up to 2 by 4 by 3 cm., located in the left and right frontal, right parietal, and right temporal cortices; in the cerebellum, half of the right cortex was destroyed and occupied by red necrotic material, and there was a large hemorrhage in the pons. The heart weighed 300 gm. There was slight arteriosclerosis of the coronary arteries and aorta, but all coronaries were patent. No thrombi were found in peripheral vessels. The lungs showed evidence of chronic passive hyperemia. There was hyperemia of the stomach, pancreas, and large and small intestine. The liver weighed 1,925 gm. and showed evidence of chronic passive hyperemia. It cut with increased resistance, the capsule was normal, and the cut surface was firm and a reddish brown, with a fine, pale brown honeycombed appearance and much free blood. The spleen weighed 700 gm. and had a smooth gray capsule. It cut with the usual resistance, to reveal bulging, and a moderately firm parenchyma which was dark red with no evidence of lymph follicles or trabeculae. None of the lymph nodes were enlarged or unusual. The kidneys and ureters were normal in appearance. The ribs, sternum, vertebrae and femora showed dense cortical gray bone of normal thickness and were filled with diffusely soft, bright red marrow, less trabeculated than usual. In the femoral shafts the marrow extended the entire length of the bone and into epiphyses, where it was still dark red and very soft.

Microscopic sections of the important organs revealed, in addition to hyperemia of all organs, hemorrhage and necrosis in the brain areas described, without evidence of thrombosis. The liver showed generalized fatty metamorphosis. Neither liver, kidneys nor lymph nodes showed evidence of myeloid infiltration. The spleen showed marked granulopoiesis, with many adult polymorphonuclear leukocytes but no myeloblasts. Bone marrow showed hyperplasia of both erythroid and myeloid elements, "consistent with a diagnosis of polycythemia"; the erythrogranulocytic ratio was 1:2; there were many normoblasts and rubricytes, but no megaloblasts; there was no increased number of myeloblasts, and megakaryocytic, eosinophilic and basophilic series were normal. No spinal cord sections were made.

Discussion

Variation in Normal Response to Liver: Adequate therapy with vitamin B_{12} completely corrects the hematologic defect of patients with addisonian pernicious anemia. One might expect treatment to be followed by rises above the average normal value of 5.0 million in some cases, since Wintrobe [34] indicates that the red blood cell count may rise in a healthy male to 6.2 million

without being regarded as above normal limits. This was the case in Minot and Murphy's [24] original report of the specific response to liver, in which three of 45 patients showed repeated levels of red cells above 6.0 million. Reduction of liver dosage was followed by a reduction of red count in all cases. However, the administration of large doses of liver extract or vitamin B_{12} does not cause an increase in red blood cell count above the upper limits of normal in normal persons or in patients with pernicious anemia.

Polycythemia Following Treatment with Liver Extract: Emil Weil [32] reported two patients with pernicious anemia who showed red cell levels of 6.8 and 7.9 million after oral therapy with liver extract. Koessler and Maurer [20] have also remarked that some patients show red counts above 5 million after liver, and Geriola [14] reported a case showing a transient rise to 7 million after therapy. Hogler [18] observed a patient with pernicious anemia who showed a rise in red blood cell count from 1.4 to 11.0 million after splenectomy and liver therapy. Leukocytes were 13,000 at the time of maximal erythrocytosis. More recently Ferrary [12] reported one case of pernicious anemia treated with liver that showed a rise of 1.6 to 10.6 million red cells per cubic millimeter, with 131% hemoglobin. Reduction of the dose was followed by fall to normal levels, and a further increase in dosage was not attempted again.

However, Birnie [5] in 1936 described a case which alternated between pernicious anemia and polycythemia, depending on therapy. The patient had achlorhydria and a macrocytic anemia of 1.76 million red blood cells per cubic millimeter, which rose to 11.0 million after liver. After phenylhydrazine the red cell level fell to 2.0 million, and subsequently rose to 5.6 million per cubic millimeter after liver therapy was resumed. The leukocyte picture was normal at all times. Goldstein [15] also mentioned several cases of alternating pernicious anemia and polycythemia that had been reported to him by physicians, and Castle [7] followed a similar case for several years.

A somewhat more complex disorder was mentioned by Minot and Castle [23] in a patient who had the typical neurologic symptoms of pernicious anemia with a red blood cell count of 6.0 million per cubic millimeter. On liver therapy the count rose to over 9 million per cubic millimeter, and he suffered from occlusive vascular phenomena. Reduction in liver was followed by a return of neurologic symptoms. This is the only report of symptomatic polycythemia after liver in pernicious anemia. Bauer [4] also spoke of a patient treated with oral liver who developed an erythremia that persisted despite cessation of therapy and subsequent exacerbation of neurologic signs. In none of these reported cases is mention made of the marked leukocytosis, or splenomegaly, so characteristic of polycythemia rubra vera, and in none is a polycythemic death reported.

However, Galt, Hunter and Hill [13] reported a case of pernicious anemia that was superseded by polycythemia of extreme degree two months after B_{12} therapy. Their case continued to be polycythemic after cessation of therapy, developed an enlarged spleen with normal bone marrow, and required phlebotomy and radioactive phosphorus. Two month follow-up revealed normal hematologic values.

Other polycythemic responses have been reported within four months following the use of B_{12} but none has had characteristics of polycythemia vera, and none has progressed to death.[3, 29]

Anemia and Leukemia Following Polycythemia: The converse of the above

cases, that of polycythemia eventuating in pernicious anemia, has been reported: Strauss [31] used liver in treating pernicious anemia developing after polycythemia vera and obtained a reticulocyte response and return to polycythemia.

Polycythemia rubra vera and pernicious anemia have both been known to eventuate in chronic myelogenous leukemia.[6, 8, 11, 16, 17, 19, 26] A markedly elevated white count is part of the usual clinical picture of polycythemia vera, and terminally it may surpass 50,000 leukocytes per cubic millimeter, with such a marked shift to the left that it is indistinguishable from myeloid leukemia. Distinction is made on the presence or absence of myelogenous infiltration of liver, spleen, kidneys and other organs, rather than on bone marrow examination. Polycythemia may also be present during the incipient stages of typical chronic myelogenous leukemia, but the terminal picture is usually one of profound myelophthisic anemia.

Relation Between Pernicious Anemia and Polycythemia Vera: These reports offer little to explain the mechanisms involved in the coexistence of polycythemia and pernicious anemia. Many attempts to link the two diseases etiologically have been made. Christian [9] in 1925 pointed out the frequent clinical similarity in the presenting symptoms of the two disorders, but emphasized the differences in gastric acidity, which is normal or increased in polycythemia and decreased in pernicious anemia.

Subsequent investigators have proposed a gastrogenic hypothesis for the two disorders, invoking a markedly increased production of intrinsic factor in the one and a decrease in the other. This theory has been based on inadequate data, such as (1) attempted treatment of polycythemia vera with gastric lavage; (2) increased frequency of peptic ulcer in polycythemia vera; (3) alleged increase in antipernicious anemia activity of the gastric juice of patients with polycythemia vera; and (4) animal experiments suggesting a greater reticulocyte response following injection of gastric juice from polycythemic patients than normals or patients with pernicious anemia.[1, 25, 33]

This gastrogenic theory of polycythemia vera has been discredited by a number of observations. Normal persons have shown no rise above normal erythrocyte levels despite massive doses of liver.[31] In the patients of Castle and Minot there was achlorhydria with polycythemia vera. Since the isolation of vitamin B_{12} the defect in pernicious anemia has been more firmly established, but the nature of polycythemia vera remains unknown. Castle [7] considers that it is best explained by Reznikoff's theory,[28] which proposes generalized bone marrow anoxia because of vascular changes in the vessels of the marrow. Wiseman [35] considers it a neoplastic condition, because of the great similarity to and coexistence with leukemia.

Mechanism in the Present Case: In this present patient, the pernicious anemia is well established by the evidence of achlorhydria, megaloblastic bone marrow, neurologic signs and macrocytic anemia, all responding to liver in a man who was well nourished and not an alcoholic. The only certain pathologic proof—cord sections—unfortunately was not obtained. However, several factors are atypical, among them the persistently elevated leukocyte count, splenomegaly and hepatomegaly, all in the presence of a relapse occurring during therapy which probably was not adequate. Administration of ineffective or deteriorated liver preparations has been known to be followed by relapse, and is indicated in this patient by marked and sustained response to vitamin B_{12}. The

leukocytosis during relapse is distinctly unusual, since leukocyte counts are usually below 5,000 per cubic millimeter at that time, and there is evidence of a defect in white blood cell production as well as in red cell production. The leukocytosis was noted even before the onset of anemia, as well as after response to therapy, but no abnormal forms were ever found peripherally, and there was no evidence of leukemia at post mortem. The bone marrow findings were never suggestive of agnogenic myeloid metaplasia, the other condition that might present such a picture.

The terminal picture here was characteristic of typical Vaquez-Osler polycythemia rubra vera, although a definite diagnosis cannot be made as in the case of the pernicious anemia. Erythrocyte, hemoglobin and leukocyte levels were markedly elevated, and both spleen and liver were enlarged. Dehydration, without clinical evidence of it, could not cause hemoconcentration to such a degree as was observed here. Bleeding tendencies, the cause of death in this case, were also characteristic, but no thromboses occurred. Platelets were adequate on smear, and the bleeding time and clot retraction were both reported as normal, in spite of the increased capillary fragility. The course was extremely short for Vaquez's disease, which is usually chronic in nature. Death is often the result of cerebrovascular accident, which occurred early in the course of this patient's polycythemia. The marked leukocytosis here was not thought to be a primary leukemia because of (a) the inability to find increased myeloblasts in the marrow at a time of marked peripheral leukocytosis; (b) the absence of abnormal cells in the peripheral blood at any time, and (c) the lack of myeloblastic infiltration of organs at postmortem examination.

In this case, as in other reports, it is probable that the patient had two separate disease entities, one of which was unable to express itself in the presence of the other. Thus, it can be postulated that this man had the potential for developing polycythemia vera, and that only the leukocyte elements were capable of proliferating while there was lack of vitamin B_{12}. Only after this defect in the erythropoietic apparatus was repaired was he able to respond to the polycythemic stimulus and develop the clinical state causing his death. The mechanism of polycythemia vera remains unexplained but appears unrelated to gastric causes.

Summary and Conclusions

1. A case is described of pernicious anemia eventuating in polycythemia vera after vitamin B_{12} therapy, and the pathologic findings are reported.
2. The literature concerning such a response to liver extract is reviewed.
3. The coexistence of the two disorders is thought to be coincidental.

Summario in Interlingua

Es describite le caso de un masculo blanc de 58 annos de etate qui disveloppava polycythemia mortal post administrationes de vitamina B_{12} como tractamento de anemia perniciose. Le patiente habeva essite tractate durante quatro annos con raffinate extracto hepatic pro un anemia megaloblastic macrocytic que esseva associate con achlorhydria e neuropathia peripheric. Leucocytosis habeva essite presente durante le integre intervallo de quatro annos, per contrasto con lo que es usual in casos de leucopenia.

In decembre 1949 un recidiva hematologic e neurologic occurreva. Isto se corrigeva post administrationes de vitamina B_{12}. Le patiente recipeva injectiones de vitamina B_{12} un vice per mense usque a augusto 1950. Un mense plus tarde le hemoglobina esseva normal, sed un marcate leucocytosis polymorphonuclear esseva constatate. In novembre 1950 le patiente suffreva un accidente cerebrovascular, e il esseva constatate que le hematocrite monstrava un valor de 79 pro cento. Nulle tendentia hemorrhagic esseva detegibile. Le morte interveniva 16 dies plus tarde.

Le necropsia revelava multiple areas de hemorrhagia e necrosis in le cerebro. Le hepate e le splen esseva allargate, sed nulle allargamento de nodos lymphatic esseva notate e nulle infiltration leucemic in ulle organo. Le medulla ossee esseva hyperplastic. Nulle thromboses in vasos peripheric esseva detegite.

Un revista del litteratura revelava le previe occurrentia combinate de anemia perniciose e polycythemia in le mesme patiente. Le nivello del numeration sanguinee ha frequentemente essite relationate al dosage de hepate. Depost le discoperta de vitamina B_{12}, plure casos de responsa polycythemic a vitamina B_{12} ha essite reportate. Le caso del presente reporto es le prime mortal.

Le existentia de anemia perniciose e de polycythemia ver in iste patiente es considerate como un coincidentia, sed il es interessante specular que forsan le carentia de vitamina B_{12} preveniva le disveloppamento complete del polycythemia.

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PAROXYSMAL VENTRICULAR FIBRILLATION IN THE ABSENCE OF OTHER DISEASE*

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Ventricular fibrillation was first clinically demonstrated on a dying heart.[1] Since that time it has been held to be a sign of grave prognostic significance. For many years it was described chiefly as an accidental finding demonstrated on an electrocardiogram at the time of death. However, scattered cases appeared in the literature in which the patient did not die immediately after onset of

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fibrillation. The series of Parkinson [2] first demonstrated that ventricular fibrillation could be a cause for Adams-Stokes syndrome. In a recent review of Adams-Stokes syndrome caused by paroxysmal ventricular fibrillation,[3] 51 cases were found up until 1952. Average duration of life following diagnosis in these cases was nine weeks; however, one patient survived as long as seven years. It is of especial interest that an atrioventricular conduction defect was noted in 38 out of 50 patients in this series.

The above described facts are generally known; it is less commonly appreciated that paroxysmal ventricular fibrillation may appear in the absence of other demonstrable disease. This should not be surprising, since the related condition of paroxysmal ventricular tachycardia appears not rarely among people who are otherwise well. In the series of Armbrust and Levine,[4] 13 patients out of 107 gave no evidence of heart disease other than a paroxysmal ventricular tachycardia. Cooke and White [5] found that five out of 22 with paroxysmal ventricular tachycardia were otherwise normal. It is then perhaps to be expected that, as sufficient cases of paroxysmal ventricular fibrillation are accumulated, some of them will appear in patients without other disease.

The first such case was described by Dock [6] in 1929. This patient was completely normal with the exception of having had fainting spells all his life. An electrocardiogram taken during an episode of syncope was characteristic of ventricular fibrillation. The patient recovered spontaneously without any sequelae. He was then given an injection of epinephrine which precipitated another episode of fibrillation. The waves were somewhat more formed than during his spontaneous attack, but the complexes varied greatly from one heart beat to the next and were too irregular to be called anything other than fibrillation.

Bjerlov [7] reported a 22 year old electrician who had an episode of rapid heart action while at work. The rate varied from 180 to 330 per minute, and lasted at these levels for 22 hours. A diagnosis of ventricular fibrillation was made at that time, but review of the tracings suggests that the rhythm might be classified as ventricular flutter. There was no history of illness in this patient, and no physical defect could be found. However, he was working on an electric cable in an underground, poorly ventilated area with a gas soldering lamp, and it is possible that the fibrillation was precipitated either by inhalation of a toxic gas or by an electric shock.

A 50 year old white male with several attacks of paroxysmal ventricular fibrillation, one proved by electrocardiogram, was described by Bechgaard [8] in 1948. This patient gave a history of rheumatic fever at age 28, but there were no signs of rheumatic damage on physical examination, and he had been asymptomatic since that time. Following the diagnosis of paroxysmal ventricular fibrillation he remained symptom-free for a year, at the end of which time he died suddenly. An autopsy was completely negative. There was no evidence at all of any damage to the heart, and a diagnosis of death due to ventricular fibrillation was made.

In 1949 Moe [9] presented a case of a 38 year old male with ventricular fibrillation. This patient was of considerable interest because on electrocardiogram he demonstrated ventricular fibrillation followed by two normal sinus beats and then beats resembling the sinus ones but with no preceding P wave. This patient's T waves remained normal during the attack but flattened the next day,

then returned to normal after three days. It was suggested that the pathogenesis of the fibrillation in this case was hyperirritability of the heart plus AV block. This patient has remained healthy and was still alive at the time of the report, three years after the diagnosis was made.

A final case is that of Storstein,[10] who described a 37 year old, otherwise healthy male who had multiple attacks over a very short period of time. The diagnosis of paroxysmal ventricular fibrillation was proved on electrocardiogram, and the patient recovered completely in spite of the fact that he had been given injections of adrenalin and benzedrine before the diagnosis was established. This patient was alive and healthy four years after his attack, at the time the report was written.

Case Report

First Hospital Admission: A 17 year old negro male was first admitted to the John Gaston Hospital on June 24, 1951, after a short episode of unconsciousness. He stated that he had suffered from "spells" during his early childhood but remembered nothing of their nature. On several occasions during the month prior to admission he had become dizzy and faint, then had cried out and lost consciousness. Consciousness always returned in a matter of a minute or two, leaving him without symptoms but extremely frightened. He was brought to the hospital immediately after one of these attacks. Close questioning revealed that he could usually predict the onset of an attack by a few minutes, chiefly by the means of a sensation of fear. He had not noted any antecedent irregularity of the pulse. Since the attack was terminated by unconsciousness, he did not know whether the rhythm reverted to normal abruptly or gradually. There was no visual or auditory aura. He never bit his tongue, or voided or defecated involuntarily during these episodes. He stated that he considered himself in excellent health. He indulged in the usual sports appropriate to a boy of his age, and did not have any difficulty during strenuous exercise.

With the exception of the above mentioned "spells," he knew of no past illness. Specifically, there was no history suggestive of congenital heart disease, rheumatic fever or diphtheria. He denied taking any medication, and there was no known exposure to toxic substance. Family history was non-contributory.

Physical examination revealed a tall, well developed, well nourished negro male. The examination was normal with the exception of the cardiovascular system. The heart was not enlarged, and the heart sounds were normal. A soft, blowing, grade 1 systolic murmur was audible at the apex. The rate was 52 per minute, the rhythm basically regular, with occasional ventricular premature contractions. The blood pressure was 122/76 mm. of Hg.

Laboratory: Complete blood counts were normal. Sedimentation rate measured .3 and .4 mm. maximal fall per minute. Admission urinalysis revealed 2 plus proteinuria, which persisted in lesser degree throughout hospitalization. Serologic test for syphilis was negative. X-ray of the chest showed the heart to be normal in size and contour. The lung fields were clear. The electrocardiogram taken in the Emergency Room at the time of admission showed a basic sinus rhythm, atrial premature contractions, paroxysmal right bundle branch block (in aVR only), and abnormally broad T waves with what were felt to be large U waves (figure 1).

Hospital Course: The patient was given sedatives but continued to have occasional attacks. These episodes started with a scream, following which the patient arched his back and thrashed around in bed but did not convulse. He sweated profusely and stopped breathing for about 30 seconds. Each episode lasted about three minutes. Following return of consciousness he appeared light gray in color, in

contrast to his normal dark brown, and was extremely apprehensive. Immediately following such an attack he was conscious of cardiac irregularity but had no other complaints. Small doses of phenobarbital were given, and no further episodes were noted after the first 48 hours of hospitalization. Serial electrocardiograms revealed gradual disappearance first of the premature auricular contractions, then of the paroxysmal right bundle branch block, but there was no significant change in T or U waves. He was discharged on July 27, 1951.

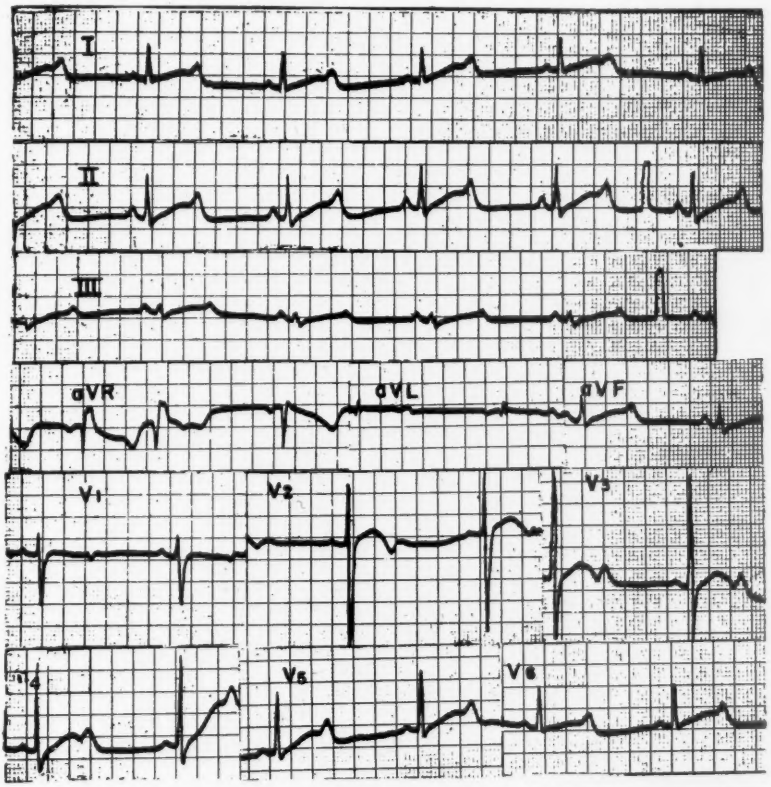

FIG. 1. Admission electrocardiogram, June 24, 1951, demonstrating sinus bradycardia, paroxysmal right bundle branch block and atrial premature contractions, and prominent T and U waves.

During the next six weeks he was followed in the Outpatient Department. He had no complaints. Physical examination remained negative, and the electrocardiogram did not change.

Second Hospital Admission: The patient was re-admitted to the hospital on September 5, 1951, complaining of gas on the stomach. This caused pressure on his heart and was followed by a fluttering sensation of the heart. These symptoms had started about three hours prior to admission but had gradually increased in severity. Physical examination was unchanged from the previous admission except that the cardiac rhythm seemed regular. Laboratory studies again revealed albuminuria.

Complete blood count and erythrocyte sedimentation rate were normal. Fasting blood sugar was 92 mg. %; glucose tolerance, normal; serum calcium, 10.7 mg. %; serum inorganic phosphorus, 4.0 mg. %. Cardiac fluoroscopy and an upper gastrointestinal series were normal. Electro-encephalogram was normal.

Hospital Course: The patient had a definite fainting spell the afternoon following admission. The next evening an attack occurred in the presence of the intern,

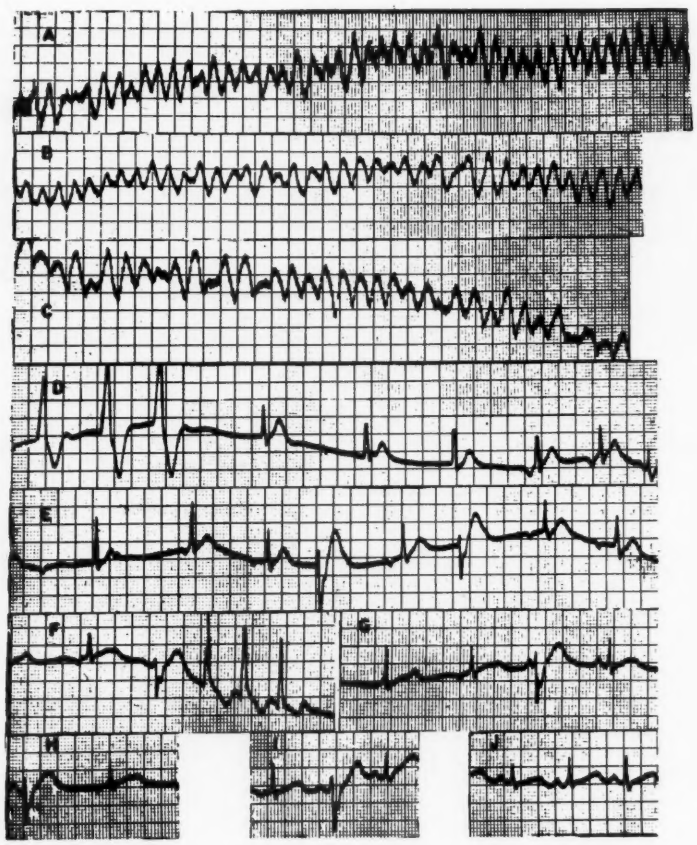

FIG. 2. Electrocardiogram taken during syncopal attack, September 7, 1951:
A–C: Segments of continuous tracing recorded over three-minute period of syncope.
D–J: Tracings at one-minute intervals following disappearance of fibrillation.

who immediately attached electrocardiographic electrodes. By the time the machine was turned on, however, there was a normal sinus rhythm. The electrodes were left in place on the patient. Five minutes later the patient was again heard to scream. No cardiac activity could be detected clinically. Electrocardiogram at that time revealed a paroxysmal ventricular fibrillation over a three-minute period (figure 2). This subsided on the administration of approximately 500 mg. of Pronestyl intravenously. He was then given Pronestyl, 500 mg. every four hours. During the

next few days he had several mild spells, but no abnormality was noted by the hospital personnel. After a week Pronestyl was discontinued and quinidine, 0.2 gm. four times a day, was instituted. He was discharged on September 25, 1951, after an asymptomatic two weeks.

The next five months he was followed by the Outpatient Department. He had no further symptoms of any nature.

Third Hospital Admission: He was admitted to John Gaston Hospital for the third time on February 20, 1952, for electrolyte study. Calcium was found to be

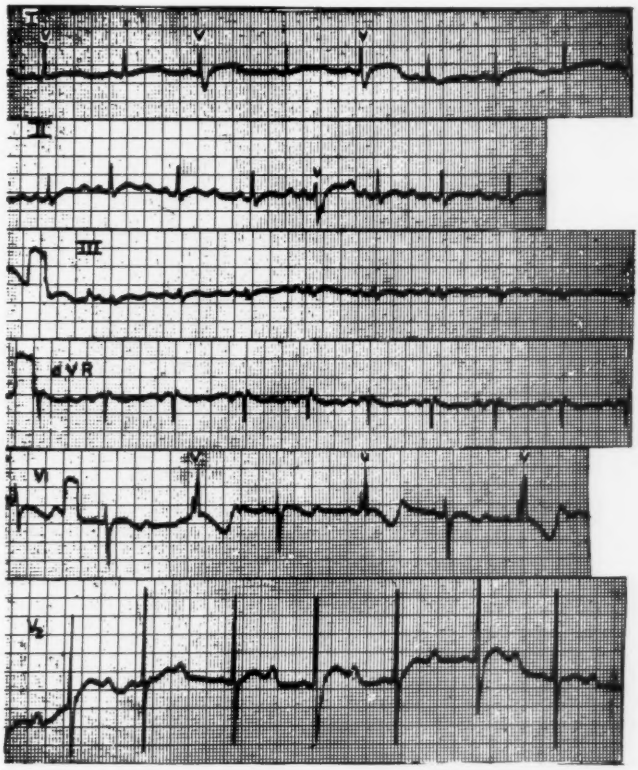

FIG. 3. Electrocardiogram taken on January 5, 1953, following syncopal attack. Note intermittent right bundle branch block (marked by arrow).

11.2 mg. %; phosphorus, 3.6 mg. %; albumin, 5.0 gm. %; serum sodium, 148.8 mEq./L.; potassium, 4.9 mEq./L.; chloride, 108.7 mEq./L. Electrolyte content of the red blood cells was normal. An infusion of 10% glucose with 30 units of regular insulin was given in order to observe the effects of lowered potassium on the electrocardiographic pattern. Potassium dropped to 3.7 mEq./L., but the electrocardiogram was unchanged.

The patient was seen later at approximately monthly intervals in the cardiovascular clinic. All medications were stopped, but he had no recurrence of symptoms.

Fourth Hospital Admission: On January 5, 1953, he was readmitted to the hos-

pital because of syncope. He stated that he had had no attacks since the last clinic visit, six weeks previously, until the day prior to admission, at which time he fainted once. The second episode occurred immediately before he was brought to the hospital.

Physical examination revealed only a very frightened young man. With the exception of 3 plus proteinuria, admission laboratory studies were negative. Serum sodium was 143.8 mEq./L.; potassium, 4.5 mEq./L.; chloride, 95.5 mEq./L.; red cell sodium, 10.9 mEq./L.; potassium, 103.4 mEq./L.; chloride, 49.6 mEq./L.; serum

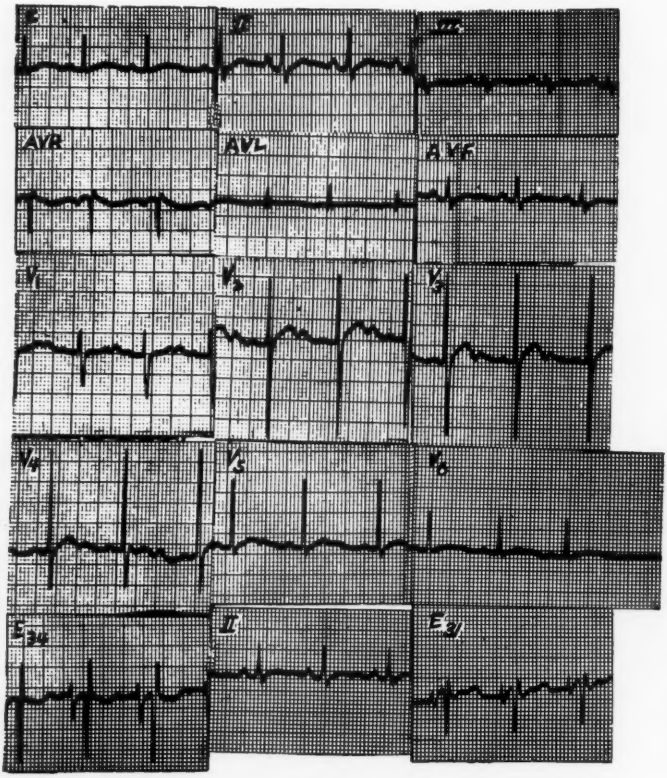

FIG. 4. Electrocardiogram taken on March 9, 1955. Esophageal leads fail to demonstrate abnormal or blocked P waves. (The last three strips were taken in very rapid succession.)

calcium, 10.6 mg. %; albumin, 5.3 gm. %. The electrocardiogram was unchanged (figure 3).

Late on the evening of admission the patient complained of dizziness and faintness. He was examined by the resident, who found no abnormality. The pulse was 54 and regular. After about two minutes of increasing apprehension he suddenly cried out and began to breathe deeply and stertorously. He did not convulse. No pulse could be felt, and no heart sounds were audible. After about 30 seconds the radial pulse could again be palpated. Beats were irregular in rate and force. Within

a minute, rate and rhythm had returned to their baseline state. He was given 300 mg. of Pronestyl at once, and then quinidine, 0.2 gm. four times a day. He had no further difficulties on this regimen, although occasional ventricular premature contractions were noted. There were no electrocardiographic changes. A cardioangiogram was normal, although the left side of the heart was never well demonstrated. He was discharged on January 15, 1953, on a maintenance dose of quinidine.

He was seen at irregular intervals during the next two years. After 14 months without symptoms he stopped taking quinidine. No change was noted thereafter. He continued symptom-free until March 9, 1955, at which time he noted rapid, irregular heart action during a tooth extraction. This extraction was being done under local anesthesia, and adrenalin had been added to the anesthetic agent. Some irregularity persisted after the extraction into the evening, when he again experienced a severe irregularity and rapidity of the pulse. He did not lose consciousness at this time, nor did he become as severely frightened as on previous occasions. Electrocardiograms taken that night and next morning showed no significant changes since the previous tracings. Esophageal leads failed to demonstrate abnormal or blocked P waves (figure 4). The only other abnormality found was again the presence of albuminuria. Kidney studies were done at this time and were otherwise entirely normal. The albuminuria was not related to posture. Nonprotein nitrogen was normal, urine concentration test was normal, and intravenous pyelograms revealed no abnormality. Serum sodium, potassium, chloride, calcium and phosphorus were all normal. Since this most recent episode the patient has agreed to continue taking his quinidine, and has remained asymptomatic for a period of 12 months.

Discussion

The chief clinical causes of ventricular fibrillation are irritation of the ventricle in myocardial infarction, and passage of electric current through the heart (electrocution). Fibrillation is common as a terminal event, regardless of the basic cause of death. In addition, trauma to the heart, either direct or indirect, may precipitate fibrillation. Finally, certain organic gases may cause this arrhythmia; of greatest medical importance among these are benzene, chloroform and cyclopropane.

The mechanism and nature of ventricular fibrillation were discussed by Wiggers [11] in his classic article in 1940. He found that, while small animals might spontaneously recover from ventricular fibrillation, this is almost irreversible in large animals, and he felt that recovery was certainly rare in man, even when the ventricles were entirely normal. Experimentally he found that either premature ventricular contractions or ventricular fibrillation could be caused by stimulating the ventricle during the terminal 0.06 second of systole, the period of supernormal excitation. Any part of the ventricle could be stimulated in order to cause these abnormalities. The presence or absence of fibrillation depended upon the intensity of the stimulus; with a stimulus of lesser strength, only premature ventricular contractions occurred. It was not necessary to pass current through the entire heart, nor was sensitization with nerves or epinephrine necessary, though these measures did reduce the threshold for ventricular fibrillation.

Wiggers described four stages of ventricular fibrillation experimentally, many of which can be frequently recognized on study of clinical electrocardiograms. The first, or undulatory stage, lasts one to two seconds and consists of three to

six undulatory contractions with the characteristics of premature systoles. Wiggers explained the first beat as being a premature contraction, with the others being due to a reëntry phenomenon. Following this is the second stage of convulsive incoördination, which lasts 15 to 40 seconds. The waves are more frequent and spread over smaller areas of ventricle. The ventricle seems to pull about in a convulsive manner. The third stage is that of tremulous incoördination and lasts two to three minutes. The ventricle consists of smaller and smaller, independently contracting areas. Electrocardiographic waves are quite small and irregular. Finally, there is the stage of atonic fibrillation marked by regional block and failure of contractility. There are slow feeble wave lengths over short distances, followed by slow passage of waves over the interventricular septum.

Clinically it has been noted that paroxysmal ventricular tachycardia usually takes place in the presence of altered atrioventricular conduction. That this is also true in these cases without evidence of organic heart disease is suggested by the case of Moe,[9] in which P waves were absent following the episode of ventricular fibrillation. An examination of the recovery electrocardiogram (figure 2) of the patient described in this report reveals that P waves returned only slowly following the cessation of the fibrillation and, where first appearing, were ectopic in nature; this is suggestive of an SA block.

Treatment of this condition may be either electrical or chemical. The efficacy of electric defibrillation [12] has been abundantly demonstrated both experimentally and clinically in recent years. During an acute attack of fibrillation this is the treatment of choice, since the circulation cannot be depended on to take intravenously administered chemicals to the heart. Both quinidine and procaine amide have been suggested as therapeutic agents; Schwartz [13] feels that both are contraindicated if there is evidence of established A–V dissociation.

The present case is being presented as paroxysmal ventricular fibrillation in the absence of other heart disease; however, it is immediately apparent that the patient's resting electrocardiogram is not normal. Exactly what the abnormal T and U waves mean cannot be definitely stated. These waves are certainly suggestive of electrolyte imbalance, but repeated efforts to demonstrate this have been fruitless. Similar U waves have been seen following attacks of paroxysmal tachycardia;[14] however, the waves in the present case persist even after long asymptomatic intervals. It has been suggested that the waves following the ventricular complexes in the 1951 electrocardiograms represent blocked P waves rather than U waves, variations in timing from that of a perfect two-to-one block being explained on a positive chronotropic effect.[15] However, in view of the similarity of these waves to those seen in the 1955 tracing (figure 4), which cannot on the basis of esophageal leads represent atrial activity, and their lack of resemblance to other P waves in the same lead, this diagnosis does not seem likely.

A further point of interest in this case is the fact that the patient has premonitory sensations. No definite abnormality has ever been demonstrable, either clinically or on electrocardiogram, at the time the patient first becomes frightened. Yet he does become frightened about two to three minutes before the clinical onset of cardiac irregularity. An attractive hypothesis to explain this would be a sort of cardiac epilepsy. However, the lack of normal cerebral control over the ventricle, plus the normal electro-encephalogram, militates against this.

Summary

Five cases of paroxysmal ventricular fibrillation in the absence of other disease have been reviewed. A sixth case presenting this finding has been described, and the mechanism of ventricular fibrillation discussed.

Acknowledgment

The author wishes to express thanks to Dr. Eugene Lepeschkin for his helpful comments.

Summario in Interlingua

Es presentate un breve revista de cinque casos de paroxysmal fibrillation ventricular in le absentia de altere morbos, que es trovate in le litteratura. Un sexte caso, in un juvene masculo negre, es presentate in detalio. Durante le intervallos inter le attaccos de fibrillation nulle anormalitates esseva trovate, excepte un grande unda U in le electrocardiogramma. Le patiente es mantenite con quinidina. Ille es asymptomatic depost cinque annos. Le mechanismo de fibrillation ventricular es discutite.

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PERIPHERAL VASCULAR OCCLUSION DUE TO HEMORRHAGE IN HEMOPHILIA*

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INTRODUCTION

HEMORRHAGE into soft tissue secondary to hemophilia is a rare cause of peripheral vascular occlusion. Seven cases of hemophilia with this complication leading to gangrene have been previously reported.[1, 2, 3, 4, 7, 10, 11] Operative treatment was used in all and resulted in loss of either life or limb. Newer methods of therapy are now available and allow a more rational and more conservative approach. The present case of hemophilia is reported not only for its rare complication but also to demonstrate the successful outcome of conservative management. To our knowledge, it is the first reported case of hemophilia with peripheral vascular occlusion and demarcation of the affected limb that has survived without amputation.

CASE REPORT

A 22 year old unemployed white male was admitted to Bellevue Hospital on August 11, 1954, with the chief complaint of pain in the right leg for one day.

The patient was a known hemophiliac, the disease having been discovered at birth following an episode of bleeding into the gastrointestinal tract. Throughout his life, many hemorrhagic complications had occurred, including multiple hemarthroses, hemoptysis, epistaxis, rectal bleeding, melena and hematuria. Nevertheless, the patient had not been disabled by the disease, and lived a normal life.

The patient's maternal grandfather, four maternal uncles and his sister's son were known to have hemophilia. He had one male and one female sibling, both free of the disease.

One day prior to admission the patient was kicked in the right shin in a barroom scuffle. After the injury he spent a restless night because of increasingly severe throbbing pain in the right leg. On awakening he found the right leg below the knee to be swollen and warmer than the left. He sought admission because of continued pain.

Physical examination revealed a temperature of 99° F.; pulse, 80; respiratory rate, 20; blood pressure, 150/90 mm. of Hg. The patient complained bitterly of pain in the right leg. The right calf and foot were swollen and very tender, without redness, pitting edema or heat. There was a 1 by 2 cm. ecchymotic area over the shin. The knees showed slight joint deformity without limitation of motion, presumably due to old hemarthrosis. The physical examination was otherwise negative.

Laboratory examination revealed: urine, negative; hemoglobin, 15.5 gm.%; red blood cells, 5.0 million; hematocrit, 43%; white blood cells, 6,800, with 62% polys, 3% bands, 25% lymphocytes, 8% monocytes, 1% eosinophils and 1% basophils. The platelets on smear were adequate in number. The erythrocyte sedimentation rate

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was 7 mm./hr.; nonprotein nitrogen, 30 mg.%; Mazzini test, negative. Stool guaiac test was negative. The clotting time was 35 minutes (Lee-White method) and the bleeding time was two minutes. Tourniquet test was negative, and clot retraction was normal. Chest x-ray was negative. Roentgen examination of the right knee revealed subcondylar cystic changes in the lateral condyle of the femur and the lateral portion of the tibial plateau. X-rays of other joints were within normal limits.

The patient was placed on bed-rest, Demerol for pain, and local cold packs to the leg. The use of more specific therapy was withheld at first in the hope that the bleeding would not progress.

The following morning the right leg below the midcalf had become cold, pulseless and cyanotic, and the soft tissues were "woodyhard" from the popliteal space to the Achilles tendon. There was a sensory defect to all modalities over the medial side and plantar surface of the right foot. The patient was given two units (500 c.c.) of fresh frozen plasma, with reduction of the clotting time to 11.5 minutes. The surgical consultant advised either needle aspiration of the tissues filled with blood or splitting of the fascia to relieve the pressure and thereby restore the arterial circulation. Because of the poor results obtained by surgical intervention in previously reported cases, operation was deferred and a plan of conservative management outlined. Accordingly, the leg was packed in ice, reflex heat applied, and whiskey (30 c.c. every three hours) and Priscoline (50 mg. every four hours) were given. The head of the patient's bed was elevated by means of 6″ blocks under the bed legs. Terramycin, 250 mg. four times a day, was added. The use of tobacco was prohibited.

On the third hospital day there was a sharp demarcation at the ankle, with a cold, pulseless, cyanotic foot. Fever rose to 101.8° F. The leg was wrapped in vaseline gauze and a protective cotton dressing applied. Two more units of fresh frozen plasma were given. There was steady improvement over the next three days, with gradual return of color, and one week after admission the peripheral pulses again became palpable. On the eighth hospital day the urine urobilinogen was positive in the 1:64 dilution. This value rapidly returned to normal. During the second hospital week the clotting time rose to 42 minutes, without evidence of further bleeding. The only residuum was a 1 by 1 cm. ulceration from pressure over the lateral malleolus, which healed promptly. Return of full muscle power was aided by extended physiotherapy in the form of whirlpool baths and active exercises. The patient was discharged ambulatory on September 17, 1954, to be followed with continued physiotherapy.

Discussion

Occlusion of peripheral arteries due to pressure from bleeding into tissues in hemophilia is a complication rarely reported. As shown in table 1, the outcome in the previously reported cases was poor. This is particularly true in those cases seen before the use of the Cohn fraction. The advent of antihemophilic globulin, fresh frozen plasma, fresh whole blood and antibiotics will certainly improve the result of therapy.

At present the therapeutic emphasis seems to be on surgical intervention in this type of case. The newer modes of therapy mentioned above would, superficially at least, seem to lessen the hazards of surgery. However, two points are worthy of note here: (1) the fascia splitting operations or needle aspirations to drain hematomata are often ineffective, because usually the hemorrhage is diffuse in the muscle and not localized to fascial spaces; (2) persistent bleeding following surgery may and often does occur at a time when the clotting time is normal or near normal as a result of therapy with antihemophilic globulin.[5]

Because of the difficulties attendant upon surgical therapy, it would seem wise to consider conservative therapy [6, 9] for acute arterial occlusion. This consists of elevation of the head of the bed, reflex heat, vasodilators, and meticulous care of the soft parts of the involved extremity. Specific antihemophilic agents should be used where indicated, keeping in mind that refractoriness to their action may develop rapidly.[8]

TABLE 1

Summary of Previously Reported Cases

Year	Author	Sex	Age	Location	Therapy	Outcome
1856	Erichsen[1]	M	34	Left leg	Aspiration Fascia-splitting operation Amputation	Died
1918	Starker[2]	M	14	Right leg	Hematoma drained	Died
1932	Blalock[3]	M	39	Right arm	Amputation	Lived
1936	Firor and Woodhall[4]	M	16	Right thumb	Aspiration Amputation	Lived
1943	Echternacht[10]	M	13	Left leg	Amputation	Died
1953	Crandon et al.[11]	M	5	Right foot and leg	Excision of popliteal space Amputation for gangrene	Lived
1954	Schuster[7]	M	25	Left leg	Amputation	Lived

The good result obtained in this case may be due to the great variability of hemorrhage into limbs, but it also suggests that conservative management is effective. Surgical therapy may be unnecessary and even detrimental.

SUMMARY

A case of arterial occlusion secondary to hemorrhage into the soft parts of the leg is reported as a rare complication of hemophilia. A review of the literature reveals uniformly poor results in surgical management of these cases. The successful outcome in this case following conservative therapy suggests that this approach may be the method of choice in the handling of these cases.

SUMMARIO IN INTERLINGUA

Es reportate le caso de un hemophiliaco mascule de 22 annos de etate qui disveloppava un occlusion arterial peripheric in le gamba dextere, secundari a un hematoma traumatic. Le tractamento esseva conservative. Illo consisteva de calor reflexe, compressas de glacie, elevation del capite del lecto, e Priscolina, insimul con plure infusiones de plasma congelate fresc. Le restablimento esseva gradual sed complete, e nulle intervention chirurgic esseva effectuate.

Le revista del litteratura indica que isto es un complication rar in casos de hemophilia. Solmente septe simile casos ha previemente essite reportate. Illos omnes esseva tractate chirurgicamente, e le resultatos esseva uniformemente pauco bon. Ex le total de septe patientes, tres moriva e le alteres perdeva le membros in question per amputation. Viste iste pauco incoragiante experientia in casos comparabile al nostre, nos nos sentiva stimulate a essayar un therapia conservative pro le occlusion arterial e a utilisar le plus moderne drogas que es disponibile pro combatter le symptomas hemorrhagic in casos de hemophilia. Le excellente resultatos obtenite in le caso del

presente reporto pare indicar que le supra-describite therapia es valide e debe esser prendite in consideration in futur problemas de ist genere.

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TREATMENT OF LEUKEMIA CUTIS WITH DEMECOLCIN *

By Edward Shanbrom, M.D., and Daniel Kahn, M.D., *West Haven, Connecticut*

Although at the time of this writing there have been no original reports in the American literature on the use of demecolcin ("Colcemide"-Ciba) in leukemia, the drug has had considerable use in Europe. The only report in the English literature appeared in the *British Medical Journal* in April, 1955, by Leonard and Wilkinson.[1] There have been several interesting reviews in the European literature on the effect of demecolcin in various neoplastic conditions.[2, 3, 4, 5, 6, 7] Although the drug exhibits some antimitotic action in a variety of neoplasms, it is the consensus of all authors that demecolcin is most useful in chronic granulocytic leukemia.

Demecolcin (desacetylmethylcolchicine) is an alkaloid of *Colchicum autumnale,* and differs from colchicine itself by the simple replacement of an acetyl group on the side chain by a methyl group. Experimental evidence [8, 9, 10] demonstrates that it inhibits mitosis in metaphase, but its toxicity appears to be 30 times less than that of colchicine. Unlike other cytotoxic agents used in the treatment of

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The demecolcin ("Colcemide") used in the treatment of this patient was generously supplied by Dr. John Saunders, of the Ciba Pharmaceutical Co.

leukemia, its action on hemopoiesis is a unique selective inhibition of granulocyte production, and often there is an associated temporary thrombocytosis. Whether these newly formed thrombocytes are physiologically active is not clear at this time. The erythrocytes appear to be relatively unaffected by demecolcin, and only rarely have decreases in reticulocyte formation been noted.

There has been some success in using demecolcin in acute granulocytic leukemia [1, 3, 5] and some suggestive benefit in Hodgkin's disease and other tumors; on the other hand, most authors agree that it may be harmful in lymphocytic leukemia. The best therapeutic results are seen in chronic granulocytic leukemia, and are characterized by a striking improvement in general clinical condition, increase in appetite, rapid decrease in splenomegaly, and a diminution in the total number of granulocytes. The remissions are short lived if the drug is stopped, lasting a few days to several weeks, while a prolonged remission may be obtained by continued maintenance therapy. The drug may be administered orally or intravenously, a more rapid effect being achieved by the latter route and with smaller doses. The dosage of demecolcin is not well established but ranges between 1.0 mg. and 15.0 mg., an average daily dose being 5.0 mg.

To date, the toxic effects of demecolcin have been minor and usually subside after discontinuing the drug. Gastrointestinal symptoms of nausea, vomiting and diarrhea, so characteristic of regular colchicum, are rarely seen with demecolcin. As is to be expected with many cytotoxic agents, spermatogenesis may be inhibited. Pruritus and alopecia have been reported in several cases, but these complications appear to be transient and disappear with the cessation of therapy.[2, 5]

The inhibition of granulopoiesis in the reticuloendothelial system by demecolcin appears well documented at this time, but the ability of the drug to exert an antimitotic effect on granulocytes in extrahemopoietic tissue has not been previously reported. The case we are about to describe not only demonstrates the potent antileukemic effect of this drug on the general hematologic picture, but also illustrates its ability to resolve metastatic lesions of granulocytic leukemia.

Case Report

A 36 year old married white male was admitted to the West Haven Veterans Administration Hospital because of cough, anorexia and fatigue of two months' duration. He was known to have had chronic granulocytic leukemia since October, 1951, and had been successfully treated with splenic radiation on two occasions. He had, in the past, received triethylene melamine (TEM) and urethane, without beneficial effect. The patient had had a satisfactory remission on myleran therapy since November, 1953, receiving 4 mg. of the drug daily. In October, 1954, his spleen began to enlarge and his white blood count increased despite an increase in myleran to 8 mg. daily. In November, 1954, he developed a cold and cough. His temperature was 102 to 103° F. There was no chest pain or dyspnea, but he felt weak and run down. He was admitted to the New Haven Hospital on December 27, 1954, with fever, splenomegaly and a white blood count of 179,000; hemoglobin was 10.5 gm.%; hematocrit, 30%. He was treated with penicillin for 11 days, with only slight improvement. His chest film revealed densities in the left lower lobe. During his admission he received 1,000 roentgen units to his spleen, with a fall in his white count to 7,400 and an increase in platelets from 62,000 to 334,000. He received 5 units of sedimented red cells. At the time of transfer to the Veterans Administration Hospital the patient felt much better and no longer had chest pain. He was still somewhat weak and

had a cough productive of one quarter cup of yellow-white sputum. It was noted that he had lost a total of 20 pounds in a period of eight weeks.

His past history was not significant except for a hospitalization in 1936 for schizophrenia, and a right orchiectomy in 1954 for an adenomatoid tumor of the testicle.

Physical examination revealed a well developed, well nourished white male in no distress, who coughed occasionally, producing yellow sputum. The patient's skin was diffusely tanned, with old radiation burns noted in the left upper quadrant of the abdomen. The conjunctivae were pale. Funduscopic examination was normal. Examination of the lungs revealed dullness to percussion, with decreased breath sounds and medium inspiratory râles at both posterior bases, extending halfway up the left lung field posteriorly. There was a soft apical systolic cardiac murmur. The spleen was easily palpated at the level of the anterior iliac spine, and was firm and tender. There was liver dullness and tenderness to percussion two fingerbreadths below the right costal margin, with no definite edge palpable. There were small, slightly tender,

FIG. 1. Patient before treatment with demecolcin, showing extensive involvement of the skin by leukemia. Note the varied size of nodules on the chest and face. The hemorrhagic character of these lesions is best seen on the lower extremities. The enlarged spleen has been outlined on the abdominal wall.

bilateral cervical and axillary nodes. There was marked tenderness of the sternum, lower left rib cage, and sixth thoracic vertebra.

Laboratory Data: On admission his white blood count was 7,400, with 50% segmented neutrophils, 1 lymphocyte, 19 nonsegmented neutrophils, 16 myelocytes, 12 blasts and 2 atypical cells; hemoglobin, 13 gm.%; hematocrit, 39%; sedimentation rate, 38 mm. Urinalysis, normal. Sputum culture revealed Neisseria species and *Hemophilus influenzae*. Serum bilirubin direct, 0.05 mg.%; indirect, 0.55 mg.%. Alkaline phosphatase, 19.3 units. Total protein, 7.1, with albumin, 3.1, and globulin, 4.0 gm.%. Cold agglutinins were negative. Uric acid was 5.43 mg.%. Several sputa for acid fast bacilli or tubercle bacilli smears and cultures were negative. Urine urobilinogen, 0.18 Ehrlich units. Urine for bile, negative. On March 30, 1955, uric acid was 7.76 mg.%. Direct and indirect Coombs' tests were negative. Stools for blood were persistently positive by the guaiac test. On May 2, 1955, nonprotein nitrogen was 40 mg.% and blood urea nitrogen was 19.8 mg.%. On May 4, 1955, the

serum bilirubin was 0.25 direct, 1.0 mg.% indirect. Coagulation time and bleeding time were normal, and clot retraction was complete within one and one-half hours. On May 3, 1955, bromsulphalein retention was 9.5% in 45 minutes. Chest x-ray on admission revealed a blunted left costophrenic angle and mottled densities in the lower lung fields bilaterally. Repeated chest films showed slight clearing of the mottled densities. An electrocardiogram was within normal limits.

Two days after admission several nodular skin lesions, about 3 mm. in diameter, were noted on the shoulders and anterior chest. A biopsy was performed which was reported as leukemia cutis.

Hepatomegaly and the elevated alkaline phosphatase suggested leukemic infiltration of the liver, while the clinical and x-ray picture was compatible with pulmonary

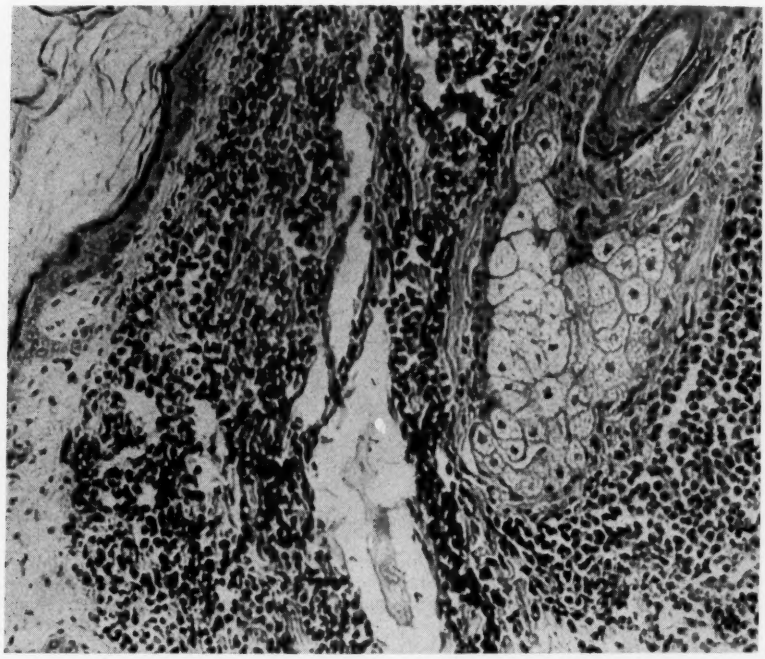

FIG. 2. Photomicrograph of biopsied skin nodule. The epidermis is intact, but the dermis is invaded by leukemic cells which form masses around sebaceous glands and sweat ducts.

leukemic spread. By February 11, 1955, the white blood count had risen to 98,000, with 16 blast cells, accompanied by a fall in the hematocrit to 30% and hemoglobin to 9.5 gm.%. The patient was started on 8 mg. of myleran daily. The white blood count continued to rise, reaching 112,000 on February 18, 1955. At that time the platelet count was 90,000, and although the patient felt subjectively stronger, his white blood count did not start to decrease until February 24, 1955, when it fell to 73,000. The white blood count continued to fall gradually, reaching 11,500 on March 8, 1955, with no essential change in the differential count. The patient continued to be febrile, and the spleen was still palpable four fingerbreadths below the left costal margin, and was moderately tender. He had a 14 pound weight loss from the time of admission;

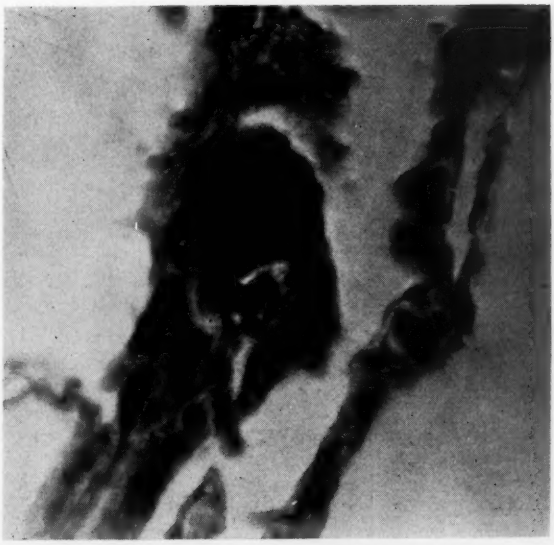

FIG. 3A. Photomicrograph of alveolar septa of lung.

more significantly, the skin lesions had gradually been increasing in severity and extent, despite the fall in white blood cell count. During this time his condition was deteriorating gradually. He was being maintained at a hematocrit level of 25% only with multiple transfusions of sedimented red blood cells. It was apparent that the myleran was not affecting the skin lesions, which had spread to involve the face,

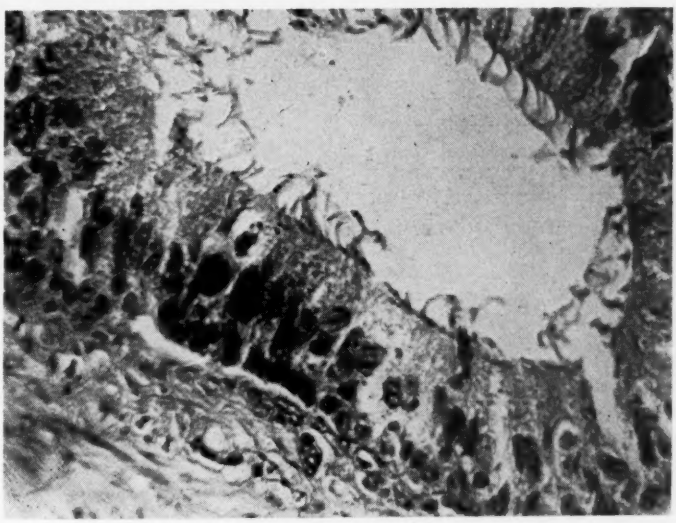

FIG. 3B. Photomicrograph of tubule of epididymis.

arms, back, anterior trunk and lower extremities. The skin was more intensely tanned. There was widespread purpura, and there were hundreds of nodular lesions with hemorrhagic bases. The patient gradually developed deafness, and examination of the oral pharynx revealed many 1 cm. yellow-white nodules, some of which were situated about the orifices of the eustachian tubes. Two weeks later the white blood count was 36,000, with 12 blast cells; hematocrit was 31%, and platelet count, 110,000. Triethylene melamine was started in an initial dose of 2.5 mg., with side-effects of malaise, myalgia and arthralgia. Despite two more 5 mg. doses of triethylene melamine at weekly intervals, the patient's white blood count continued to rise, reaching 111,000 on April 2, 1955, with a platelet count of 50,000 and hematocrit of 28%. It appeared that the triethylene melamine was exerting little effect on the hematologic picture. By April 14, 1955, the white blood count was 102,000; hemoglobin, 5.5 gm.%; hematocrit, 18%; platelet count, 20,000. This represented a precipitous fall

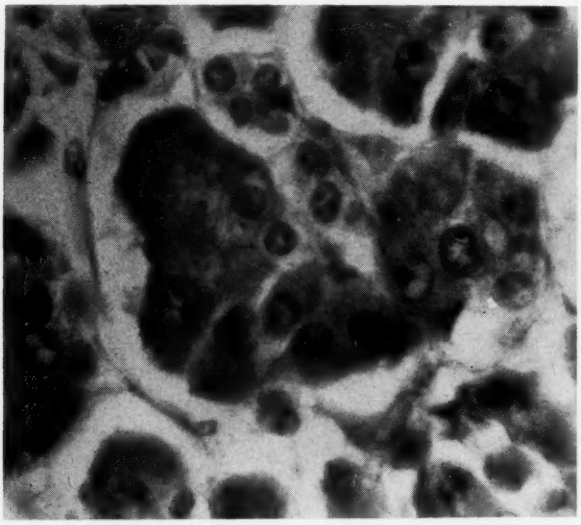

FIG. 3C. Photomicrograph of pancreatic acini, demonstrating metaplastic changes induced by demecolcin (polyploidy). Note the varying cellular and nuclear size, the prominent nucleoli and overabundance of chromatin.

in the thrombocytic and erythrocytic elements. The patient had a tachycardia of 120 and appeared hyperpneic and pale. There was a rapid downhill course, and by April 27, 1955, he appeared moribund. Cortisone was started with an initial dosage of 300 mg. daily and rapidly tapered to a dose of 25 mg. daily, so that it was discontinued after 15 days. While he was on cortisone therapy the white blood count rose to 252,000. On April 30, 1955, demecolcin was started in an intravenous dosage of 2.0 mg. daily for five days, except for 8 mg. on the fourth day. Two days after initiation of treatment with demecolcin, the white blood count was 102,000, with 7 blast forms, and by the fourth day it had fallen to 30,000, with no significant change in the differential. He was continued on 1.0 mg. doses of demecolcin orally for seven days. After 12 days of therapy the white blood count was 29,600 and the reticulocyte count was 4.6%. In view of the apparent leveling off of the decrease in white blood count, the dosage of demecolcin was increased to 9 mg. daily, orally. Four days later

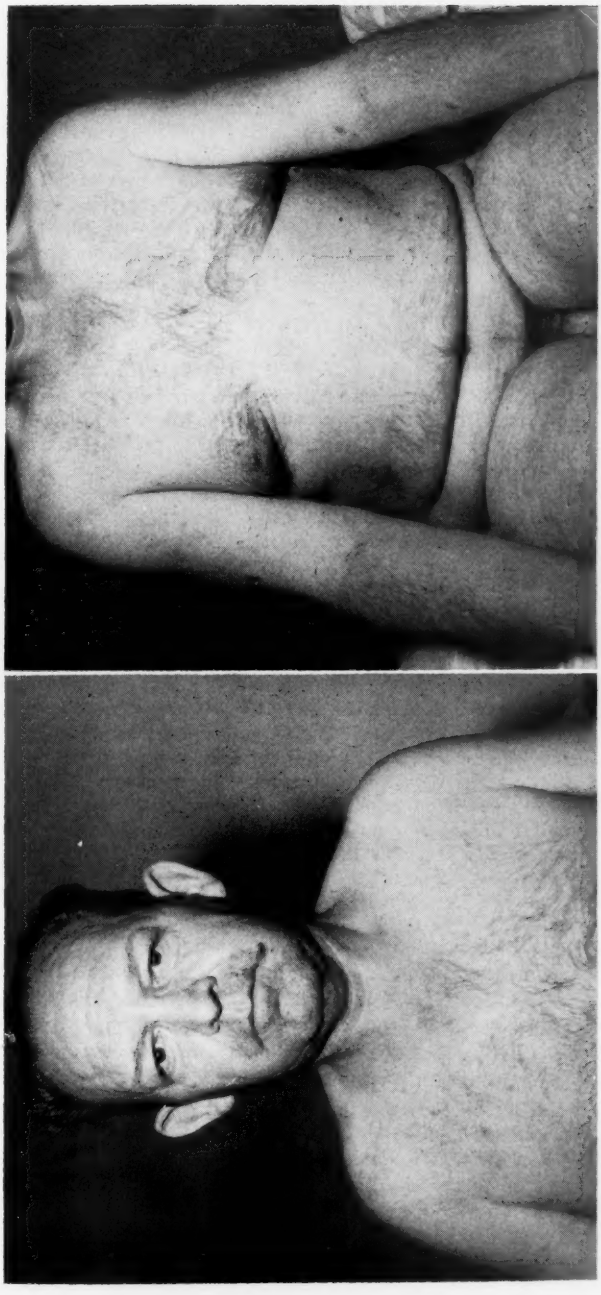

FIG. 4. *Case 2.* Discrete nodules can be seen scattered over the body. On the forehead the nodules tend to be confluent.

the white blood count had dropped precipitously to 4,300. The demecolcin was then withheld, but the leukocyte count continued to fall and remained at a level of 500 to 1,600 for the rest of his course. The other changes in his clinical condition were a remarkable decrease in size of the spleen so that it was no longer palpable, and a dramatic regression of the nodular skin and mucous membrane lesions. The patient received no further demecolcin therapy after May 16, 1955, and was maintained on an average of 2 units of sedimented red blood cells daily. His hemoglobin remained at a level of 5 gm.%, with an average hematocrit of 20% and platelet counts of 20,000. The patient felt subjectively improved, with a return of appetite and hearing. However, he became progressively cachectic and had a total weight loss of 40 pounds from the time of admission. Hemorrhagic manifestations of epistaxis, purpura and melena increased. He became confused and irrational, and after falling out of bed had persistent tonic seizures and lapsed into a coma. Lumbar puncture revealed a pressure of 180 mm. of spinal fluid, with 380 red blood cells per cubic millimeter, and he died despite energetic supportive therapy, including anticonvulsants and blood transfusions.

Autopsy Findings: The lytic effect of demecolcin on visceral lesions of granulocytic leukemia was established at autopsy. The liver, lungs and spleen showed no striking selective changes of leukemic infiltration. The spleen was enlarged (weight, 900 gm.), but not sufficiently to be palpable below the left costal margin. There was loss of lymphoid tissue throughout the body generally. The skin of the chest, abdomen and upper extremities (sites of the initial infiltration) was less extensively involved than was that of the lower extremities at the time of autopsy. The bone marrow showed regions of hyperplasia, chiefly of the myeloid elements, surrounded by areas of aplasia and fibrosis. Only one microscopic focus of leukemic infiltration was noted on examination of sections of the kidneys. All of the organs, and in particular the brain, showed extensive gross and microscopic hemorrhage, considered to be the cause of death.

The epithelium of the lungs, pancreas, kidneys, prostate and pituitary glands revealed marked atypical metaplasia. This cytology was similar in each organ. There was marked cellular hypertrophy, with proportionate increase in cytoplasm and nuclei. The nuclei were vesicular, with prominence of the chromatin and nucleoli. There was no mitotic activity or tissue invasion. These changes suggested in situ metaplasia (polyploidy), rather than regeneration following epithelial necrosis.

Of added interest in this 37 year old male with leukemia and an adenomatoid tumor of the testis in the past was the finding at autopsy of a typical small-cell prostatic carcinoma, apparently unrelated to the atypical hypertrophied cells described above.

Discussion

Although leukemia cutis is not an uncommon finding in lymphocytic leukemia, the appearance of skin lesions in the chronic granulocytic form is only rarely reported. When it appears it is considered a grave prognostic sign.[11] The largest number of cases that we have seen reported was presented recently by Costello et al.[11] On commenting on this paper, Casten[11] reviewed 70 cases of myelogenous leukemia and found 44 cases which exhibited skin manifestations. However, only seven of these were considered to be specific leukemic infiltrates, five of which showed papular or nodular lesions, so that it would still seem true that actual infiltration of the skin by leukemic cells in the chronic granulocytic disease is rare when compared to involvement of other tissues. Our patient appeared to have three distinctly different skin lesions: First, there was a diffuse tanning of the skin which preceded the appearance of the other lesions by several

days. It is quite possible that this pigmentation could have resulted from myleran therapy, since this drug has been reported to produce tanning.[12] Second, discrete macular lesions developed which generally appeared to be purpura arranged in a concentric fashion. Third, distinct skin infiltration occurred, with the formation of definite nodules throughout the body which varied greatly in size, configuration and consistency. Some were actually egg-sized! These nodules appeared, for the most part, at the site of the purpuric lesions, and eventually the base of the nodules had a circular hemorrhagic ring. Many of the lesions were stony hard and suggestive of carcinomatous infiltration, while others were softer and rubbery in consistency. Many of the nodules were tender to palpation. A fourth type of lesion appeared on the mucous membranes of the oral pharynx and consisted of whitish or yellowish white nodules about 0.5 cm. in diameter. Some of these nodules were adjacent to the openings of the eustachian tubes, and we could not help wondering if the patient's partial deafness was related to the occlusion of the eustachian tubes. The fact that his hearing improved somewhat following regression of the pharyngeal lesions with demecolcin therapy would lend support to this idea.

The management of skin lesions in granulocytic leukemia has always been unsatisfactory. Our patient had been treated with triethylene melamine and myleran, but the skin lesions progressed at their same rate in spite of these therapeutic agents. The dermatologist's therapeutic approach is well reviewed by Costello and those who reviewed his paper.[11] Cortisone appeared to be successful in one of Costello's cases, while 6-mercaptopurine had no effect in another. The use of superficial x-ray therapy or the application of a paste of radioactive phosphorus would seem undesirable to us because of the systemic nature of the disease. That demecolcin was successful in ameliorating the skin disease in our patient seems all the more remarkable in the face of the failure of myleran or triethylene melamine. Unfortunately, our patient was in extremis when demecolcin therapy was instituted, with marked thrombocytopenia and widespread hemorrhagic manifestations, so that we were unable to evaluate long-term treatment. Nevertheless, those who observed the remarkable clinical and laboratory response to demecolcin agreed that the patient was definitely though briefly "brought back from the grave."

We have discussed in detail the effect of demecolcin on the skin because we feel that it was the most striking and objective evidence of the response to therapy. Certain other clinical responses to demecolcin were also outstanding. Because of the moribund condition of the patient the drug was administered intravenously. After three days of therapy (a total of 14 mg.), the total leukocyte count dropped from 250,000 to 30,000. The differential count was essentially the same, and there was no decrease in the number of blast forms seen. The general condition of the patient improved remarkably, and although there was some improvement with the initiation of cortisone therapy, it was more striking following the administration of demecolcin. There were return of appetite, and increase in strength and sensation of well being. Although there was a moderate reticulocytosis initially following therapy, there was no reflection of this in the total red cell volume, for the hematocrit never rose. Following moderately large doses of the drug neutropenia persisted, but it was never sufficiently severe that ulcerations of the buccal mucosa occurred.

A final word should be said about blood transfusions in this case. Because the patient had received innumerable small transfusions of sedimented cells over a prolonged period without any remarkable rise in hematocrit, we decided to try large transfusions in order to avoid the theoretic bone marrow depression which might result from daily small transfusions. Our patient had obvious vascular fragility, as evidenced by the widespread hemorrhagic tendencies, and we cannot help but conjecture the possible disastrous results that may occur when the blood vasculature of such a patient is suddenly overloaded by large quantities of blood.

Summary

1. A case of chronic granulocytic leukemia with extensive skin infiltrations is presented.

2. Demecolcin was successful in causing resolution of the skin lesions which were previously resistant to all other forms of therapy.

Acknowledgment

The authors are indebted to Dr. John Rice, of the Pathology Department, Veterans Administration Hospital, West Haven, Connecticut, for his interest in this case and detailed review of the pathologic findings.

Addendum

Since the original writing of this paper a second case of leukemia cutis has been treated with demecolcin. This patient differed from the first case in that he had acute monocytic leukemia of the Naegeli type.

Case Report

A 51 year old white male shop foreman was admitted to the City of Hope Medical Center with the diagnosis of acute leukemia. He had been apparently well until four months prior to hospital admission, at which time he had a rather profound weakness and was admitted to another hospital, where he was found to be severely anemic. A bone marrow was compatible with the diagnosis of acute leukemia. He was transfused with several units of blood but received no other specific therapy. Two months later he began to note the appearance of small nodules in the skin, which he felt had developed following the administration of a "red blood cell stimulating" drug given to him by another physician. These skin nodules increased in size, number and distribution rather rapidly, but seemed to disappear, or at least to decrease in size, following transfusions.

Physical Examination: The patient was a well developed, well nourished white male, alert and coöperative, very pale, appearing chronically ill but not in acute distress. Numerous indurated nodules were noted over the skin of the entire body. These were nonpigmented, and were most concentrated on the chest and arms. They varied in size from a few millimeters to 2 cm. The forehead was covered with flat nodules. A few small cervical lymph nodes were felt bilaterally. The lungs were clear and resonant throughout. The heart was enlarged to the anterior axillary line. Tones were good, and a grade II apical systolic murmur was heard. The liver was easily felt three fingerbreadths below the costal margin; the spleen was felt in the left upper quadrant only on deep inspiration. The rest of the physical examination was within normal limits.

Laboratory Data: White blood cells, 67,000, with 22 polymorphonuclears, 24

lymphocytes, 48 monocytes, 2 bands, 3 metamyelocytes, and 1 blast; hematocrit, 24; hemoglobin, 8.15 gm.%; platelets, 150,000. Urinalysis: specific gravity, 1.005; albumin, 1 plus; 1 to 10 pus cells per high power field. Nonprotein nitrogen, 52. Serum uric acid, 10 mg.%. Biopsy of the skin nodule showed a dense infiltration by polymorphonuclear cells and monocytic cells. The patient was begun on intravenous demecolcin, receiving 5 mg. daily for five days. There was a rapid decrease in the total leukocyte count to 5,900 after one week. Although there was a decrease in the number of immature cells seen in the peripheral blood, the differential did not return to normal. The skin nodules showed a very rapid resolution within a few days. However, there was very slight systemic improvement, and the patient continued his downhill course. By the eighth hospital day he had developed a severe aphthous stomatitis. Because of this intense inflammatory reaction he was begun on ACTH, 25 units intravenously daily. The stomatitis subsided very rapidly, but in spite of this the patient continued to go downhill; he developed a fulminant uremia, and died after 20 days of hospitalization.

At autopsy, extensive leukemic infiltrations were found in the spleen, kidneys, lymph nodes, pancreas, adrenal glands and testes.

Comment: The skin lesions in this patient were strikingly similar to those of the first case. The lesions were indurated nodules which tended to be confluent on the forehead. The remarkable clearing of these lesions following demecolcin therapy clearly demonstrates the potent cytotoxic ability of this drug. The very undesirable side-effect of aphthous stomatitis which may occur with demecolcin therapy can usually be avoided by administering the drug in smaller doses. However, this patient received only 5 mg. daily for five days, a total of 25 mg., which is a relatively small amount of the material. The fact that demecolcin was able to effect regression of leukemic metastases suggests that the drug should be of value in the treatment of some cases of acute granulocytic and monocytic leukemia.

Summario in Interlingua

Es presentate un revista del actiones pharmacologic e del uso clinic de demecolcina ("Colcemido"—Ciba). Ben que le droga exhibi un certe action antimitotic in un varietate de tumores, su plus grande utilitate appare in casos de chronic leucemia granulocytic. Es reportate un caso de chronic leucemia granulocytic con extense infiltrationes cutanee durante le phase blastic terminal. Le manifestationes cutanee consisteva de diffuse bronzage (possibilemente secundari a un previe curso de therapia a mylerano), lesiones maculopurpuric, e nodulos que variava grandemente in dimension e consistentia. Occurreva in plus nodulos jalnastre-blanc, de diametros de circa 0,5 cm, in le membranas mucose del pharynge oral. Un numero de tal nodulos esseva locate al orificios del tubo eustachian con le resultato de audition defective. Le patiente esseva tractate con mylerano e triethyleno-melamino, sed le lesiones cutanee progredeva. Quando demecolcina esseva instituite, le patiente se trovava in stato terminal con marcate grados de thrombocytopenia e extense manifestationes hemorrhagic. Le droga esseva administrate intravenosemente, in doses amontante a 14 mg in le curso del prime quatro dies. Le numeration leucocytic descendeva ab 250.000 a 30.000, durante que le numeration differential remaneva constante. Occurreva un melioration remarcabile del condition general del patiente, manifeste in le retorno del appetito e un augmento de fortia e de sensation de ben-esser. Le patiente esseva mantenite con demecolcina oral, 1 mg per die, durante un total de septe dies. Proque le numeration leucocytic se habeva apparentemente fixate a un nivello de circa 30.000, le dosage diurne de demecolcina esseva augmentate a 9 mg durante quatro dies. Al

fin de iste periodo le numeration leucocytic descendeva a 4.300, e le administration del droga esseva arrestate. Tamen, le numeration leucocytic continuava descender usque a nivellos de inter 500 e 1.600, ubi illo remaneva durante le resto del curso del patiente. Le altere eventos in le condition clinic del patiente consisteva in un frappante reduction del dimension del splen e un regression dramatic del lesiones nodular del pelle e del membranas mucose. Nonobstante, le patiente deveniva progressivemente plus cachectic, e su manifestationes hemorrhagic se intensificava. Ille deveniva confuse e irrational, cadeva in stato comatic e moriva. Le necropsia revelava le potente effecto antileucemic de demecolcina in tanto que le previemente recognoscite lesiones infiltrative de pulmon, hepate, e splen habeva disparite. Esseva notate extense manifestationes de polyploidia colchicinic in le epithelio de pulmon, pancreas, renes, e glandulas prostatic e pituitari. Un constatation incidental esseva un carcinoma prostatic. Omne le organos, specialmente le cerebro, exhibiva extense grados macro- e microscopic de hemorrhagia. Le risco possibile de grande transfusiones de sanguine in patientes con obvie fragilitate vascular es discutite.

In un addendum, un secunde caso es describite, characterisate per macroscopicamente simile lesiones cutanee sed con leucemia monocytic del typo de Naegeli. Etiam in iste caso, le tractamento con demecolcina resultava in un rapide regression del lesiones cutanee sed exerceva nulle influentia favorabile super le progresso pejoratori del morbo.

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SUBACUTE BACTERIAL ENDOCARDITIS OCCURRING IN A PATIENT RECEIVING ORAL PENICILLIN AS PROPHYLAXIS AGAINST RHEUMATIC FEVER *

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INTRODUCTION

SUBACUTE bacterial endocarditis has occurred in patients with valvular heart disease following operative procedures within the oral cavity despite the use of penicillin to prevent the transient bacteremia which may occur in such situations.[1-4] In addition, bacterial endocarditis has been noted in patients receiving prophylactic penicillin against recurrent beta-hemolytic streptococcal infection. Hunter has observed one such instance in a child receiving oral penicillin.[5] Two additional cases appeared among a group of 145 subjects with a history of rheumatic fever who were receiving monthly injections of benzathine penicillin; the causative organisms were penicillin-sensitive *Streptococcus viridans.*[6] One of these patients had undergone tooth extraction without additional antibacterial therapy.

The following report describes a case of subacute bacterial endocarditis which developed during prophylactic therapy with daily oral penicillin. The organism was a penicillin-sensitive *S. viridans.*

CASE REPORT

A 23 year old white married female was admitted to the Grace-New Haven Community Hospital on May 15, 1956, with the chief complaint of fever of three weeks' duration.

Eleven years before admission the patient had had an episode of unknown duration, characterized by painful swelling of the knees and ankles. Six years later she was told that she had a heart murmur. When she was first seen in the hospital, one and one-half years before admission, cardiomegaly, aortic insufficiency, and mitral stenosis and insufficiency were noted. There was no evidence of active rheumatic fever. Nose and throat cultures were recorded as showing normal flora. In February, 1955, prophylactic therapy was instituted, with one 250,000-unit tablet of uncoated buffered potassium penicillin G daily.

The patient was seen in the Cardiac Clinic at regular intervals and it is believed that, with the possible exception of a one-day lapse, she took oral penicillin as prescribed. In March, 1955, a four-month pregnancy terminated in spontaneous abortion. There were no operative or dental procedures during the year prior to the current admission. On April 24, 1956, after 14 months of prophylactic therapy, she was seen with the complaint of chills and fever of one week's duration. During the following two weeks, despite the continuance of therapy, the patient had daily temperature elevations up to 101.8° F. Eight blood cultures were drawn during this period. One

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revealed growth of alpha hemolytic streptococci in beef heart infusion broth only; in two other cultures alpha hemolytic streptococci grew in thioglycollate broth with added penicillinase. The prophylactic penicillin therapy was then discontinued, and four of five additional blood cultures revealed alpha hemolytic streptococci. At the time of admission to the hospital, three weeks after the onset of symptoms, the patient stated that she had experienced feverish and chilly sensations and drenching night sweats for two to three weeks. There had been one shaking chill several days prior to admission.

She appeared to be healthy and was in no distress. Blood pressure, 130/40 mm. of Hg; pulse, 108 and regular; temperature, 101.8° F. There was no clubbing of the fingers, petechiae or "splinter hemorrhages." Lymphadenopathy was not noted, the ocular fundi were not remarkable, and there was no evidence of infection in the oral cavity. The lungs were clear. Examination of the heart revealed a forceful apical impulse in the fifth intercostal space at the anterior axillary line. Characteristic murmurs of aortic insufficiency, mitral stenosis and insufficiency were present. The liver and spleen were not palpable.

Laboratory data revealed a hematocrit of 40, a white blood cell count of 8,300, with a normal differential, and a sedimentation rate of 18 mm. per hour. A trace of albumin and rare red blood cells were found in the centrifuged urine sediment. Chest roentgenograms revealed cardiac enlargement, predominantly of the left ventricle. The electrocardiogram was suggestive of left ventricular hypertrophy. C-reactive protein was 3 plus, and antistreptolysin O and streptococcus agglutination titers were within normal limits. Cultures of the nose and throat were reported as "normal flora." The organism grown from the initial blood cultures was a microaerophilic, alpha-hemolytic *Streptococcus mitis*. On serial tube dilution, growth of this organism was inhibited by 0.1 unit of penicillin per milliliter.

Therapy was instituted on the second day with 1,000,000 units of aqueous penicillin every six hours and 0.5 gm. of streptomycin intramuscularly twice daily. The following day the patient was afebrile and remained so thereafter. After six days the aqueous penicillin was replaced by procaine penicillin, 1,000,000 units twice daily. There was no growth in any blood cultures taken after institution of therapy. Early in the patient's hospital course there were two episodes of left upper abdominal pain, accompanied by transient, tender splenomegaly. On the seventh day of antibiotic therapy a tender, red, raised lesion appeared on one finger tip. The patient's course was otherwise uneventful. Antibiotic therapy was discontinued after 18 days and the patient was discharged five days later.

Prophylactic penicillin therapy against rheumatic fever was reinstituted upon discharge. Repeated clinic visits during the next nine months revealed no evidence of recurrence of infection. Subsequent blood cultures have remained negative. Throat cultures since discharge have, however, revealed persistent growth of alpha-hemolytic streptococci.

Discussion

In approximately 60% of patients with subacute bacterial endocarditis a history of a predisposing factor may be obtained.[7, 8] Transient bacteremias have been noted following various operative and diagnostic procedures, upper respiratory and gastrointestinal infections, and in association with normal menses.[8–13] It has been postulated that these conditions permit bacteria to gain access to the blood stream. In the remaining 40% of patients, one can only speculate on the portal of entry. *S. viridans* is found in the intestinal tract and is the predominant organism within the oral cavity. While bacteremias have been observed following tooth extractions and the "rocking" of infected teeth, they may occur after less traumatic occurrences, such as chewing and

gum massage.[14–16] Indeed, bacteremias have been demonstrated in animals following the ingestion of food, but not in fasting animals.[17, 18]

The oral cavity is the most likely portal of entry in the case described here, but the persistence of penicillin-sensitive organisms there during penicillin prophylaxis requires further comment. Although the ability of penicillin to alter the normal flora of the mouth is well known, *S. viridans* continues to persist in a large percentage of patients. Possible explanations for this fact include (1) inadequate concentration of penicillin at the local site, (2) the development of bacterial resistance to penicillin following exposure to the antibiotic, or (3) a resting metabolic state which renders the Streptococcus insusceptible to the bactericidal action of the drug.

Bloomfield has shown that the organisms considered part of the normal flora of the mouth grow freely upon the surface of the mucous membrane, while potentially more pathogenic organisms such as the beta-hemolytic streptococcus reside more deeply within the tissues of the pharynx and tonsils.[19] For therapy to be effective against these "surface" organisms, adequate antibiotic concentrations must necessarily appear in the saliva. The peak concentration of penicillin in saliva, which is reached at about one hour, may be as little as 0.0125 unit per milliliter, with an average of 0.029 unit per milliliter, following intramuscular injection of a mixture of 100,000 units of crystalline and 300,000 units of procaine penicillin.[20] It is probable that even this level of penicillin in saliva is not reached by oral administration of the drug in prophylactic doses such as were used in the case reported here. The organism in this case was sensitive to penicillin in concentration of 0.1 unit per milliliter, and it is known that the penicillin sensitivity of most strains of *S. viridans* ranges between 0.04 and 0.15 unit per milliliter.[21] Therefore, persistence of *S. viridans* in the oral cavity of patients receiving oral penicillin prophylaxis may be explained on the basis of inadequate penicillin levels in saliva. The more successful eradication of beta-hemolytic streptococci by this means may be due to the greater sensitivity of the organism to penicillin. An alternative explanation may be that the position of the organism within the tissues exposes it to the normally higher blood levels of antibiotic.

Parenteral administration of even larger doses of penicillin, however, has not always succeeded in eliminating the *S. viridans* from the oral cavity.[22] This finding suggests the possible importance of a change in antibiotic resistance or in metabolic state of the organisms during prophylactic therapy. While it has been observed that the *S. viridans* may develop resistance to penicillin,[23] this is an uncommon occurrence, and it was not a factor in the case reported here. With regard to the possible explanation that a resting metabolic state may protect the bacteria against the action of penicillin, it has been shown that this antibiotic exerts its maximal effect against an actively multiplying bacterial population but has relatively little bactericidal influence against a more slowly metabolizing organism.[24–26]

It therefore appears that penicillin-sensitive *S. viridans* may persist in the oropharynx of patients receiving varying doses of penicillin, and that these microörganisms may gain access to the circulation by one of several described pathways. That this occurs should not suggest discontinuance of prophylactic measures in patients with valvular heart disease, but rather indicates the importance of careful interim observation of such patients.

Summary

A case of subacute bacterial endocarditis caused by a strain of penicillin-sensitive *S. viridans* is described. The patient had been receiving continuous oral penicillin prophylaxis against recurrent attacks of rheumatic fever.

Possible mechanisms are discussed by which this organism may persist in the oral cavity despite penicillin therapy and gain access to the circulation, with subsequent localization on the valvular endocardium.

Summario in Interlingua

Subacute endocarditis bacterial ha occurrite in patientes con morbo de valvula cardiac post interventiones chirurgic in le cavitate oral in despecto del uso prophylactic de penicillina. Endocarditis bacterial ha etiam essite notate in subjectos recipiente penicillina como prophylactico contra febre rheumatic.

Le presente reporto describe un caso de endocarditis a *Streptococcus viridans*, occurrente in un patiente con rheumatic morbo cardiac qui habeva recipite un curso therapeutic de penicillina oral in doses diurne de 250.000 unitates. Le patiente esseva un feminina blanc de 23 annos de etate, con insufficientia aortic e stenosis e insufficientia mitral. Le organismo causative esseva un *Streptococcus mitis* hemolytic microaerophilic del typo alpha. Un test con tubos a dilution serial monstrava que le crescentia de iste organismo esseva inhibite per 0,1 unitates de penicillina per millilitro. Therapia a penicillina e streptomycina durante 18 dies resultava in le curation del endocarditis, e nulle recurrentia del infection ha essite observate. Tamen, subsequente culturas de specimens ab le gurgite ha continuate revelar un persistente crescentia de streptococcos hemolytic alpha.

Le cavitate oral es le plus probabile porta de entrata pro le organismos in le caso del presente reporto. Le existentia de organismos penicillino-sensibile intra le bucca durante un curso therapeutic a penicillina es forsan explicabile per (1) inadequate concentrationes de penicillina al sito local, (2) disveloppamento de resistentia bacterial a penicillina post exposition a iste antibiotico, o (3) stato metabolic inactive que rende le streptococco non-susceptibile al efficacia bactericida del droga.

Il pare que un therapia antibiotic pote esser efficace contra organismos que es considerate como parte del flora normal del bucca solmente si adequate concentrationes del droga es presente in le saliva. Il es probabile que significative nivellos de penicillina in le saliva non es effectuate per oral doses prophylactic del droga. Ben que *Str. viridans* pote disveloppar resistentia contra penicillina, isto es un occurrentia incommun e non esseva un factor in le caso hic reportate. Quanto al tertie explication possibile, on ha monstrate que penicillina exerce su effecto maximal contra un population bacterial in stato de multiplication active sed ha relativemente pauc influentia bactericida contra un organismo in stato de metabolismo relentate.

Ben que il es apparente que un *Str. viridans* de genere penicillino-resistente pote persister in le oropharynge de patientes tractate con varie doses de penicillina e pote ab ibi ganiar accesso al circulation, iste facto non debe suggerer un discontinuation de mesuras prophylactic contra febre rheumatic. Illo indica plus tosto le importantia de exacte observationes interime de tal patientes.

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THROMBOTIC THROMBOCYTOPENIC PURPURA (MOSCHCOWITZ'S DISEASE): REPORT OF A CASE WITH REMISSION AFTER SPLENECTOMY AND STEROID THERAPY *

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Cases of thrombotic thrombocytopenic purpura have been rare from the time of Moschcowitz's original description in 1925 [1] up to the recent past. In a recent review Clough [2] cites 24 cases to 1950, and the literature to date now totals approximately 60. Even more rare has been the diagnosis in vivo of this syndrome; we have been able to find only six reports.[3, 4, 5, 6, 7, 8] Yet the combination of hemolytic anemia and thrombocytopenic purpura with variable and transient neurologic symptoms should specifically suggest the diagnosis. We wish to report another antemortem diagnosis and the second well documented case of prolonged remission in the literature.

Case Report

A 27 year old housewife had an upper respiratory infection in August, 1954. She was then well until early in October, 1954. On October 9, 1954, she was admitted to the Barnert Memorial Hospital with a history of one week of purpura, weakness and hematuria. The patient was afebrile; pulse, 120 per minute; blood pressure, 120/60 mm. of Hg. She was a well developed, well nourished, pale female with no icterus evident. Purpuric lesions were present on the thighs, lips and arms. There was a positive tourniquet test. No adenopathy was found, and the liver and spleen were not palpable. There was a pulmonic systolic murmur. On the day of her admission the blood showed: hemoglobin, 3.8 gm. per 100 ml.; red cells, 1,890,000 per cubic millimeter; hematocrit, 15%; white cells, 11,200 per cubic millimeter; polymorphonuclears, 78%; lymphocytes, 19%; monocytes, 2%. Urine showed microscopic hematuria; urinary urobilinogen was 1:20. Direct Coombs' test was negative. The patient received three uneventful transfusions; after a fourth she promptly became febrile and icteric. On this day her hemoglobin was 7.0 gm.; platelets, 62,000 per cubic millimeter; nucleated red cells were seen in the peripheral smear. Despite transfusions, the patient remained severely anemic, the hemoglobin dropped to 5.5 gm., and the platelets continued at very low levels. Bone marrow showed normoblastic hyperplasia, and a Turkel trephine specimen showed adequate megakaryocytes. A preparation for L.E. cells was negative. The differential diagnosis was: (1) Moschcowitz's disease; (2) idiopathic thrombocytopenic purpura plus acquired hemolytic anemia; (3) systemic lupus erythematosus.

The patient was seen in consultation by Dr. Janet Watson, who concurred in the diagnosis of thrombotic thrombocytopenic purpura. ACTH, 25 mg. daily in an intravenous drip lasting eight hours, was begun and continued for one week, without response. During this period, transient weakness of the right arm and right face was noted repeatedly. No pathognomonic lesions of Moschcowitz's disease were seen, either in the Turkel trephine specimen or in a biopsy taken through a fresh

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purpuric spot. After 20 days of steroid therapy at an increased dosage (50 mg. daily), splenectomy was done on November 19, 1954, by Dr. Theodore Bender. Microscopic studies of the spleen and attached lymph nodes confirmed the diagnosis of thrombotic thrombocytopenic purpura (figure 1). For another period of two weeks the patient remained anemic and icteric, and apparently hemolyzed most of the transfused blood. She then gradually began to improve, and the hemoglobin level was maintained and even rose with transfusions. She was discharged on Hydrocortone therapy, 40 mg. per day, on December 13, 1954, with a hemoglobin of 10 gm. and a platelet count of 130,000, some 10 weeks after admission and four weeks after splenectomy.

Post-Hospital Course: After discharge the patient received no transfusions. Her steroid therapy was gradually reduced, and was discontinued on January 21, 1955.

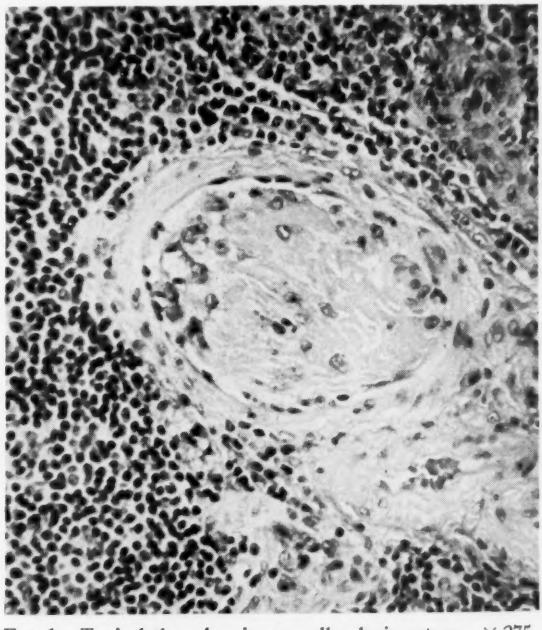

FIG. 1. Typical thrombus in a small splenic artery. × 275.

At the present time she has been without steroids for 15 months and has received no transfusions for 16 months. It is now 18 months since the onset of her disease. During this period her hematologic values have remained within normal limits, the hemoglobin fluctuating about 12 gm. and the red cell count near 4,000,000. On three occasions these values were reduced: in the postoperative period, when she developed a wound infection, the hemoglobin and red cell count were 10.5 gm. and 3,600,000, respectively; on two occasions when she had intermittent upper respiratory infection, the hemoglobin dropped to 11.0 gm. and the red cell count to 3,500,000. On all three occasions these values returned to normal as the intermittent infection cleared up. Platelets rose to a maximal figure of 454,000 six weeks after the operation and then leveled off to between 200,000 and 300,000, and did not drop with the hemoglobin and red cell count during the three episodes of infection. The white cell count has

been consistently high since operation, varying from 10,000 to 18,000. The reticulocyte count has varied between 0.8 and 3% during this time. Urinary urobilinogen has consistently been positive in 1:20 dilution, with an occasional value of 1:40.

Comment

This case represents one of the few instances of prolonged survival after diagnosis of thrombotic thrombocytopenic purpura. We have been able to find only one proved case in the literature, describing a survival of more than one year. This patient was treated one month with steroids, without any effect.[5] In our case there was no evidence of remission for two weeks postoperatively. The literature has many examples of therapeutic failures with steroids and with splenectomy. Meacham's [5] patient survived two and one-half years after splenectomy. We do not know whether the steroids or splenectomy, or both, or neither, contributed to the survival of our patient, but this is the only case we have been able to find in the literature where both splenectomy and steroids were used. We have been further impressed with one other feature of this case: Despite the excellent clinical remission, there persists a high white count, a fluctuating reticulocyte count, and a consistently present urinary urobilinogen. We feel that these, and episodes of drop in hemoglobin and red cell count with intercurrent infections, are all evidences of the persistence of a continuing disease process. Only one other well documented case [5] is reported with long-term survival, although March [9] refers to several patients who developed the syndrome terminally after prolonged illness not characteristic of this disease. Even Meacham's case was diagnosed only three months before death, after a review of slides of the spleen removed two and one-half years previously. Thus our patient offers the first opportunity for detailed investigation of an established case, and such studies are now in progress.

Summary

A case of Moschcowitz's disease diagnosed in vivo is presented. The patient was treated with steroids and splenectomy, and at present has survived 18 months after the original diagnosis. Despite clinical improvement, there is evidence of a persistent and latent disease process in this patient.

Addendum

As of August 18, 1957, the patient is clinically well 32 months after discharge from the hospital.

Acknowledgment

We wish to thank Dr. Ely Moschcowitz and Dr. Paul Klemperer for their kindness in reviewing the microscopic slides in this case.

Summario in Interlingua

Le combination de anemia hemolytic, purpura thrombocytopenic, e transiente signos neurologic in un juvene feminina suggere le diagnose de purpura thrombocytopenic thrombotic (morbo de Moschcowitz). Iste diagnose occurre sporadicamente in le litteratura, sed illo se establi infrequentemente in le patiente vivente. Ancora plus rar es le superviventia del patiente multo ultra sex a octo septimanas post le declaration del morbo acute.

Le presente reporto concerne un juvene feminina de 27 annos de etate qui se presentava con acute purpura e in qui sever anemia hemolytic e etiam purpura thrombocytopenic e transiente signos neurologic esseva constatate. Le preparato a lupus esseva negative. Le diagnose de purpura thrombocytopenic thrombotic esseva facite clinicamente, e le patiente esseva tractate, sin effectos, con steroides. Splenectomia esseva interprendite a iste tempore, e le diagnose esseva confirmate histologicamente. Post un curso prolongate de steroides le patiente experientiava remission. Iste stato ha continuate depost 18 menses, ben que nulle therapia ha essite usate depost 15 menses.

In tres occasiones in le curso de iste periodo de remission, alterationes hematologic esseva notate, inducite apparentemente per infectiones intercurrente. Es etiam a notar le persistente presentia de leucocytosis e reticulocytosis. Le autores es convincite que iste factos signala le existentia de un latente processo pathologic.

Le sol altere caso con similemente prolongate superviventia que se trova in le litteratura esseva diagnosticate solmente tres menses ante morte. Ergo, le caso del presente reporto es le prime in que il existe le possibilitate de detaliate studios durante le stato de remission, serviente le objectivo de un meliorate comprension de iste processo pathologic.

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EXTRACELLULAR HYPEROSMOLARITY SECONDARY TO HIGH-PROTEIN NASOGASTRIC TUBE FEEDING*

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HYPEROSMOLARITY exists in the extracellular fluid when the concentrations of solutes is increased above the normal range.

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The cellular membrane is considered to be relatively impermeable to the sodium ion, and for this reason the extracellular sodium concentration is much higher than is the intracellular sodium concentration. Because of this concentration gradient, the sodium ion concentration is an important factor in determining the effective osmotic pressure of the extracellular fluid,[1] and extracellular hyperosmolarity is most commonly associated with extracellular hypernatremia.

Hypo-osmolarity is a rather common clinical condition. Diarrhea, chronic glomerulonephritis, and mercurial diuresis with restriction of sodium intake are among the common situations which may be complicated by decreased osmotic pressure of the extracellular fluid due to net loss of sodium in excess of water, leading to hyponatremia.

The opposite condition, hyperosmolarity, probably occurs less frequently and is certainly less commonly recognized. Schoolman,[2] in analyzing the largest series of patients with hyperosmolarity yet reported, suggests that the syndrome be divided on a clinical basis into three etiologic categories: primary desiccation, central nervous abnormality, and the recovery phase of diabetic acidosis. Examples of desiccation and hyperosmolarity associated with high-protein nasogastric tube feeding have been reported by Engel and Jaeger.[3] We have recently had an opportunity to observe a patient with this problem. The fact that the metabolic abnormality in this patient was not recognized until relatively late in its development makes us feel that it is not well known generally. Since both the diagnosis and therapy of the disorder are relatively simple and uniformly effective if one understands the pathologic physiology, we feel that presentation and further discussion of this case are worth while.

Case Report

A fifty year old white male bricklayer was admitted to the University of Michigan Hospital with the chief complaint of dysphagia of two weeks' duration. There had been a weight loss of 10 to 15 pounds in the six weeks prior to admission. There were no other gastrointestinal symptoms. The remainder of the history was noncontributory.

Physical examination on admission was within normal limits except for evidence of mild dehydration. The blood pressure was 128/78 mm. of Hg.

The initial routine blood and urine examinations were within normal limits except for a hemoglobin of 11.5 gm. %. The stool guaiac reaction was negative. Chest x-ray was negative. An upper gastrointestinal series was reported as showing cardiospasm. Bronchoscopy was negative. Esophagoscopy showed a hard constriction at the cardia; a biopsy from this area showed changes compatible with chronic inflammation. There was no evidence of neoplasm.

The patient was treated with multiple esophageal dilatations. Because of continuing dysphagia, he was started on high-protein nasogastric tube feedings on his third hospital day. However, his dysphagia did not improve and he became progressively weaker. He was transferred to the medical service on his twentieth hospital day.

Physical examination at that time was as before except for weakness which prevented the patient from rising from his bed, marked lethargy, and extremely dry skin and mucous membranes. The blood pressure was 30/0 mm. of Hg; pulse, 80.

Table 1 illustrates the important clinical and laboratory findings. It is noteworthy that the initial serum electrolyte determinations were within normal limits shortly after admission. Coincident with the development of hyperosmolarity while on nasogastric tube feeding there was marked deterioration in the patient's clinical

condition. Of more significance is the fact that there was prompt improvement coincident with the institution of appropriate therapy, which consisted chiefly of supplying additional water.

Discussion

When the history and the physical examination are reviewed, and the increased concentration of all of the elements of the blood on the eleventh and the twentieth hospital days is noted (table 1), it is apparent that there was a loss of water in this case in amounts relatively greater than the loss of sodium and other blood elements, and that the basic abnormality was therefore dehydration.

Table 1

Pertinent Clinical and Laboratory Data

Hospital Day	Daily Intake	Output	Hematocrit	Serum Na mEq./L.	Serum K mEq./L.	NPN mg.%	CO_2 mEq./L.	Cl mEq./L.	*Urine Specific Gravity	Clinical Condition
1 to 3	Ad lib.	Not recorded		136	3.4	43	28	88		Fair
4 to 9	Tube feeding of 210 gm. protein, 2,000 ml. water, 83 mEq. Na, 179 mEq. K.									
10	Tube feeding plus 3,000 ml. Ringer's IV, 1,000 ml. 5% dextrose in water.									
11	Tube feeding discontinued. Oral fluids ad lib.			159	5.1	142	21	134		Lethargic
12 to 19	Oral fluids ad lib. (intake very low).									
20	3,500 ml. 5% dextrose in water IV.	550	50	160	5.3	133	21	125	1.025	Shock
21	5,000 ml. 5% dextrose in water IV.	1,770								
22	3,500 ml. 5% dextrose in water IV.	2,920	39	136	3.4	34	23	105	1.010	Much improved
23 to 28	Tube feeding of 70 gm. protein, 4,000 ml. water, 28 mEq. Na, 60 mEq. K.	1 to 2 L./day	33	141	4.6	*	28	105		Continued improvement

* Serum creatinine 0.51 mg. %.

If it is assumed that dehydration is the initial event in the hyperosmolarity syndrome, it follows that there must be an abnormal reaction to dehydration to have the hyperosmolarity perpetuated as it was in this case. Figure 1 depicts the postulated chain of events in our patient. Negative water balance and subsequent dehydration are the first steps. It is important to realize that in this case the major cause of the negative water balance was the increased renal solute load secondary to the protein intake of approximately 210 gm. per day, and that the negative water balance developed while the patient was receiving approximately 2,000 ml. of water daily. The solute load was further increased by the liberal amounts of sodium and potassium in the tube feeding mixture (table 1). The negative water balance occurred because there is a limit to the concentrating power of the kidneys, so that there is a minimal obligatory water loss with each unit of solute excreted. It has been estimated that the minimal amount of water necessary for excretion of 1 gm. of nitrogen by the human

kidneys is between 40 and 60 ml.[4] If we assume good gastrointestinal absorption of the formula and nitrogen balance, we can estimate that our patient had an obligatory water loss of 1,650 ml. for nitrogen excretion alone. If one adds to this 1,650 ml. the obligatory loss of water associated with the excretion of other urinary solutes and the insensible loss of water, it will no doubt easily exceed the daily intake of water (approximately 2,000 ml.). Our patient was therefore in persistently negative water balance while he was receiving the high protein diet through the nasogastric tube. The inevitable consequences of the resulting dehydration are shown in figure 1 as decreased extracellular volume and hyperosmolarity. There is evidence that indicates that there is decreased renal excretion of sodium with dehydration;[5, 6] this would of course tend to increase the hyperosmolarity.

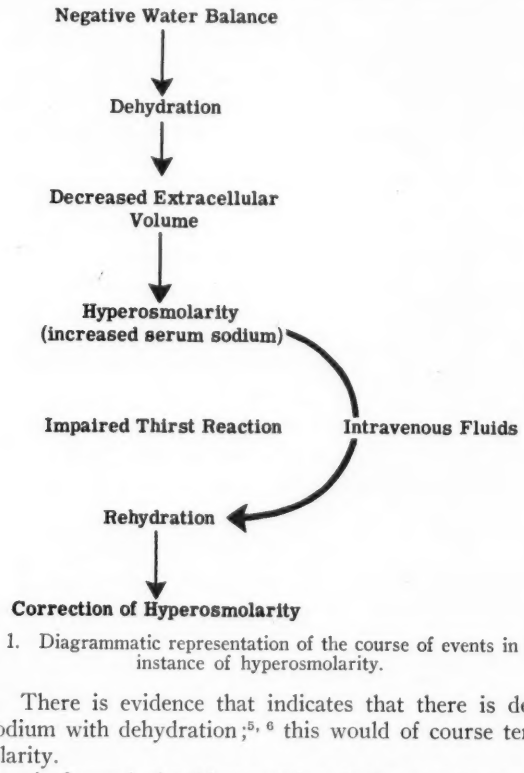

FIG. 1. Diagrammatic representation of the course of events in this instance of hyperosmolarity.

The next step in figure 1, the thirst reaction, is the most important and might be called the "corrective stage." If the mechanisms in this stage are impaired, persistent and progressive dehydration and hyperosmolarity may develop. There is an increased output of the antidiuretic hormone of the posterior pituitary in response to the hyperosmolarity.[7] This promotes conservation of water by maximally enhancing the resorption of water by the distal tubules, and by doing this tends to correct the hyperosmolarity. However, as noted before, there was a large obligatory water loss in our patient even with maximal concentration. If, then, the water output cannot be further diminished, it follows that there must be an increase in fluid intake if water balance is to be restored. In the normal individual, water intake is increased through the thirst reaction. As

indicated in figure 1, hyperosmolarity is the main stimulus for thirst in this situation, although there is some evidence that decreased extracellular volume may also stimulate thirst.[8, 9] We feel that our patient initially responded to the hyperosmolarity with thirst, but was unable to satisfy his thirst because of his obstructive esophageal disease. The dehydration and hyperosmolarity therefore progressed, with gradual deterioration in the patient's clinical condition, including impairment of his state of consciousness and circulatory collapse. As noted in table 1, the high-protein nasogastric tube feedings were discontinued on the eleventh hospital day, after seven consecutive days of administration, and the patient was then placed on oral fluids ad lib. For the next nine days the ward notes indicate that the oral fluid intake was in the range of 1,800 to 3,000 ml. per day, but on close questioning of the patient and the ward attendants it became apparent that little if any of this fluid was actually ingested, and that most of it was used for mouth wash. This no doubt explains why the patient's hyperosmolarity remained uncorrected when he was transferred to the medical service on the twentieth hospital day. Correction of his water deficiency at that time by the intravenous administration of large amounts of 5% glucose in water, as indicated in table 1, was followed by prompt and striking improvement.

We feel that this case represents an important untoward reaction to a simple and what is frequently thought to be a completely innocuous therapeutic measure, high-protein nasogastric tube feedings. However, this should not be construed as a condemnation of high-protein tube feeding. We merely wish to point out that, like all other therapeutic procedures, it must be used with certain precautions. The patient must have adequate and sometimes large amounts of water to balance the high obligatory renal water loss associated with the increased renal nitrogen excretion secondary to the high protein intake. If the feeding formula does not contain sufficient water (as in the full-strength mixture of one widely used commercial preparation), and if, because of impaired consciousness and/or mechanical defects preventing water ingestion, the patient is unable to increase his water intake through the thirst reaction, then dehydration and hyperosmolarity will develop. Hyperosmolarity may be prevented easily by lowering the protein: water ratio in the formula. This is well illustrated by the fact that our patient tolerated the tube feeding well when the protein was decreased and the water content was increased. One could safely have increased the water without decreasing the protein, because it has been shown that high-protein feeding is well tolerated if enough water is supplied.[10] Once encountered, the hyperosmolarity is as easily treated as it is prevented. Large amounts of fluid without sodium are required, the exact amount as indicated by serial determinations of the blood electrolytes, the urinary specific gravity, and the clinical response of the patient.

Summary

A case of extracellular hyperosmolarity secondary to high-protein nasogastric tube feeding is presented. The pathologic physiology, prophylaxis and treatment are briefly reviewed.

Summario in Interlingua

Dishydratation e hyperosmolaritate extracellular pote resultar ab alimentation per tubo nasogastric a alte contento de proteina, mesmo si le aqua del mixtura ali-

mentari non es multo inferior al requirimentos usual. Isto occurre a causa del alte carga de soluto renal que resulta ab le alte concentration de proteina e electrolytos in le mixtura alimentari. Le potentia concentratori del renes non es illimitate, de maniera que un alte carga de soluto renal require un minimo obligatori de perdita de aqua in le renes. Quando le perdita insensibile de aqua es addite a iste perdita renal, le resultato pote esser un negative balancia de aqua. Si le patientes es incapace a corriger le perdita de aqua per satisfacer un reaction de sete, il seque le possibilitate del disveloppamento de un persistente progressive dishydratation e hyperosmolaritate. Choc e azotemia prerenal pote occurrer.

Iste anormalitate es facile a prevenir per rememorar se que le ingestion de aqua debe esser augmentate quando le carga de soluto renal es augmentate.

Le dishydratation e le hyperosmolaritate es tractate per corriger le deficit de aqua.

Es presentate un caso illustrative.

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PANCREATIC INSUFFICIENCY AND HYPERPARATHYROIDISM *

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The most frequent cause of hyperparathyroidism is an adenoma of a parathyroid gland. The course of events leading to adenoma formation in the para-

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thyroids, as in other tissues of the body, is unknown. In some organs, conditioning factors can be identified which seem to predispose to the formation of such tumors. For example, in the thyroid gland, iodine deficiency produces hyperplasia and nodule formation, and on occasion functionally active adenomas appear. The possibility has been considered that a similar train of events sometimes precedes the appearance of a parathyroid adenoma.[1] In conditions such as rickets, osteomalacia and renal insufficiency, where the serum calcium is low, there is hyperplasia of the parathyroid glands. When such hyperplasia is maintained for a long period of time, one might expect the occasional appearance of a parathyroid adenoma.

Chronic renal insufficiency with phosphorus retention is the most common cause of parathyroid hyperplasia, and, rarely, hyperparathyroidism may ensue. However, the appearance of a functionally active parathyroid adenoma has not been reported. The next most frequent cause of parathyroid hyperplasia in the adult is osteomalacia, which in this country is usually the result of sprue or pancreatic insufficiency. Conceivably these diseases might lead to the formation of a parathyroid adenoma because of their chronicity.

The case described here is believed to represent hyperparathyroidism secondary to pancreatic insufficiency. Although nephritis was also present it was not thought to be a contributing factor. The patient also had gout.

Case Report

A 37 year old Air Force noncommissioned officer was admitted to Walter Reed Army Hospital in December, 1952, with the diagnosis of hyperparathyroidism with osteitis fibrosa generalisata.

Nine years before admission he had had an attack of tonsillitis. Two urinalyses at this time showed a trace of albumin and a few red blood cells, white blood cells and casts. Recovery was uneventful.

Eight years before admission he had suffered a sudden attack of severe retrosternal and epigastric pain with nausea, vomiting and fever. At exploratory laparotomy hemorrhagic pancreatitis was found. The patient's postoperative course was stormy and his recovery slow. During convalescence repeated urinalyses disclosed traces of albumin, particularly in afternoon specimens, and occasional hyaline casts. Repeated Addis counts showed hematuria. The maximal urine concentration was reduced, but phenolsulfonphthalein excretion was normal. The diagnosis of chronic glomerulonephritis was made. Thereafter the patient was well except for a period of mild diarrhea lasting some eight months, five years before admission. Later the patient also experienced an episode of ravenous appetite with no change in weight. There were no other symptoms suggestive of pancreatic insufficiency, sprue syndrome or diabetes mellitus. There were no symptoms attributable to renal disease.

In October, 1952, glycosuria was discovered during a routine physical examination. Although the patient was asymptomatic, he was admitted to another hospital for evaluation. The blood pressure was elevated. There were noticeable irregularities on the surfaces of both tibiae. A small nodule could be palpated behind the left sternocleidomastoid muscle at the level of the lower pole of the thyroid gland.

X-rays demonstrated generalized demineralization of the skeleton. In addition, there were cystic areas in the cortices of the tibiae, fibulae, femora, radii, ulnae, phalanges and ribs. No pseudofractures were noted. Dental x-rays showed the lamina dura to be absent about the roots of most of the teeth. On abdominal films spotty calcification was noted throughout the region of the pancreas. No glycosuria was present, and the blood sugar was normal. The serum calcium and alkaline

phosphatase were elevated, and the serum inorganic phosphorus was depressed. The diagnosis of hyperparathyroidism was made.

The patient was transferred to Walter Reed Army Hospital in December, 1952. The physical, x-ray and laboratory findings recorded above were confirmed. Additional laboratory findings were as follows: red blood cell count, 4,000,000 per cubic millimeter; hemoglobin, 12.5 gm. %; white blood cell count, 5,000 per cubic millimeter, with a normal differential. The gastric acidity was normal. A bone marrow aspiration was normal. The erythrocyte sedimentation rate was 10 mm. per hour. Urinalyses showed traces of albumin, but no sugar. The sediment contained a few red and white blood cells, but no casts. Maximal urine concentration was 1.018. Phenolsulfonphthalein excretion was normal, but endogenous creatinine clearances were slightly depressed, averaging 80 c.c. per minute. The blood urea nitrogen was

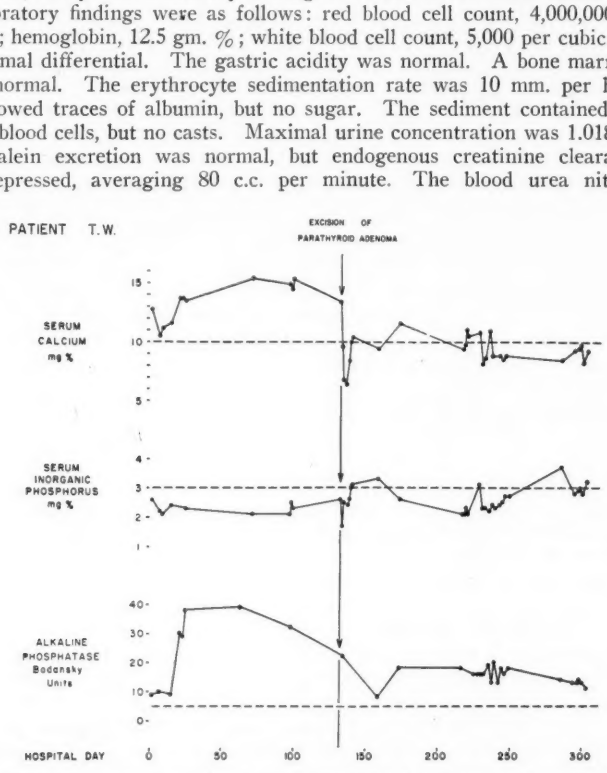

FIG. 1. Changes in serum calcium, serum inorganic phosphorus and serum alkaline phosphatase during the patient's hospital stay.

normal. An excretory urogram was normal. After a week on a low calcium diet containing approximately 200 mg. calcium per day, the patient excreted between 300 and 400 mg. of calcium per day in the urine. He was maintained on a low calcium diet until operation.

A month after admission the patient's right knee became swollen, warm and painful over a few days' time. The joint was extremely tender and contained fluid. This arthritis was accompanied by mild fever and a minimal leukocytosis. Although symptomatic treatment was of some benefit, the arthritis persisted for three weeks, spreading to involve both feet.

On February 18, 1953, the patient's neck was explored surgically. A 2 cm. tumor, near the left lower pole of the thyroid gland, was removed. Two separate, normal-appearing parathyroid glands were identified. Histologic examination of the tumor showed it to be composed of sheets of polygonal cells with abundant eosinophilic cytoplasm and round vesicular nuclei. These cells were distributed irregularly within large lobules separated by coarse strands of fibrous tissue. In a

few areas the cells tended to form acini. The histologic diagnosis was parathyroid adenoma of the chief cell type. After operation the serum calcium fell to as low as 6.4 mg. %, but the patient had no overt tetany. During the evenings of the fourth and fifth postoperative days he described a "buzzing feeling" in his hands and feet. These attacks were relieved by intravenous injections of calcium gluconate. Except for these attacks the patient had no symptoms referable to any disturbance of calcium metabolism (figure 1).

On the day after operation the patient again developed acute arthritis of the right knee, with subsequent involvement of the right foot and left knee. The reappearance of arthritis after operation suggested the diagnosis of gout. The serum uric acid was found to be moderately elevated (6.2 and 7.1 mg. %). (Stored sera, obtained near the time of the previous attack, were found to have an uric acid concentration of 10 mg. %.) Colchicine administration produced marked improvement in the arthritis within 24 hours, although residual pain and swelling persisted for nearly a month. Colchicine was continued for four months. There was no further recurrence of arthritis, but hyperuricemia persisted.

After operation the patient was given a high calcium diet, which was maintained except during special studies. The serum calcium rose quickly to normal. The serum inorganic phosphorus rose, but did not reach normal. The alkaline phosphatase remained high. A month after operation x-ray examination showed no change in the bone lesions. A bone biopsy from the crest of the ilium at this time still showed osteoclastic activity. Mild osteoblastic activity was also present, but not of the marked degree one would expect in the phase of bone repair that should follow removal of the tumor. The histologic picture was consistent with osteitis fibrosa generalisata. Three months after operation x-rays showed slight but definite recalcification, but there had been no further improvement six months after operation.

Throughout the patient's hospital stay he showed labile hypertension. On returning from pass the morning blood pressures were as high as 190/140 mm. of Hg. After a week of rest on the ward the pressures were in the normal range. There were no significant changes in blood pressure or in renal function before and after operation.

Metabolic Studies: Studies of pancreatic function were carried out three months after operation. Fasting blood sugars and oral glucose tolerance tests were normal. The serum amylase and lipase were normal, but duodenal secretions did not hydrolyze protein or starch. The amount of feces eliminated daily was slightly greater than normal, averaging 300 gm. per day, but was not changed by administration of pancreatin. The fecal nitrogen excretion was increased, averaging 4.6 gm. per day, decreasing to 3.2 gm. with pancreatin therapy. Fecal fat varied from 5 to 18 gm. per day on an intake of 65 gm. per day. Although this is greater than normal, there was no change when pancreatin was given. Prothrombin times were slightly prolonged, but were unchanged after pancreatin. An oral vitamin A tolerance test showed a fasting serum vitamin A level of 35 μg %, rising to 53 μg % three hours after ingestion of an oily preparation containing 100,000 units of vitamin A, but falling thereafter to fasting levels. In a normal subject studied simultaneously the levels rose from 47 μg % to a maximum of 102 μg % at six hours. After pancreatin administration, the patient's fasting level was 66 μg % and rose to a peak of 110 μg % nine hours after vitamin A ingestion.

Calcium infusion tests [2, 3] were performed one month before and three months after removal of the parathyroid adenoma. After the patient had been on a low calcium diet for six days, the serum levels and urinary excretion of calcium and inorganic phosphorus were measured, before, during and after the intravenous infusion over a three hour period of 10 mg. per kilogram of calcium, as calcium gluconate, in 0.9% sodium chloride solution. Before operation the infusion of calcium raised the

serum calcium appreciably, and produced an increment in the urine calcium equal to 20% of the amount infused (figure 2). There was a slight rise in the serum phosphorus; the 24 hour urine phosphorus excretion was reduced 4% from the control value. The tubular reabsorption of phosphorus, calculated from the creatinine clearance, serum phosphorus and phosphorus excretion, showed no significant change from a control rate of 60% of the filtered load. After operation the infusion of calcium caused no change in the serum calcium, and only 9% of the dose was excreted. A rise of 0.8 mg. % occurred in the serum phosphorus; the 24 hour urine phosphorus decreased 16%. The tubular reabsorption of phosphorus increased from a control rate of 70% to as high as 86%.

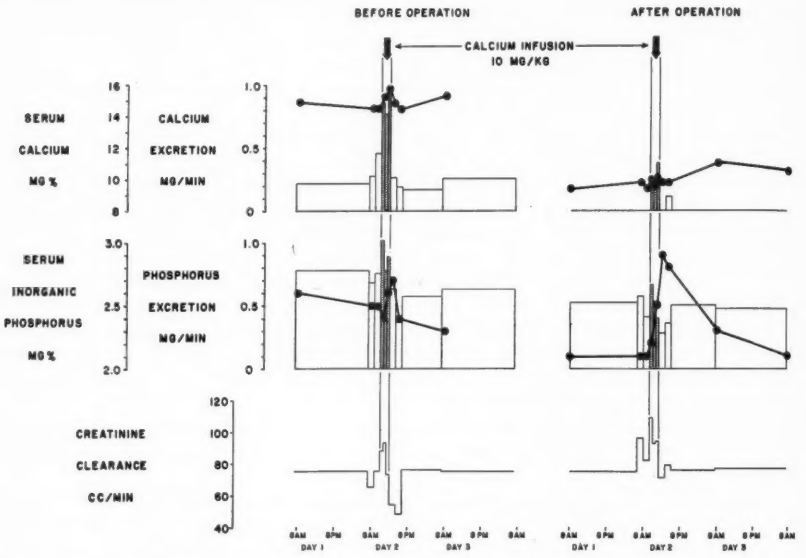

FIG. 2. Results of calcium infusion tests before and after excision of parathyroid adenoma.

Four months after operation there was only slight x-ray evidence of recalcification of the bones, the alkaline phosphatase was still elevated, and the serum inorganic phosphorus was still slightly depressed. It was felt that these continuing evidences of bone disease might have been caused by deficient calcium absorption related to pancreatic insufficiency. A study was therefore undertaken to measure the balances of nitrogen, calcium and phosphorus during a basal low calcium diet, and with the successive addition of 8 gm. of calcium gluconate per day, and of pancreatin in dosage stated by the manufacturer to provide enzyme activity equal to 12 gm. per day of the standard preparation. A month and a half later the effects were determined of the addition of calciferol, 100,000 units per day, to the basal diet plus pancreatin.

By reference to figure 3 it can be seen that after equilibrium was established the patient retained nitrogen at the rate of 1.8 gm. per day. When pancreatin was added the positive nitrogen balance increased further to 4.5 gm. per day. Pancreatin was continued through the second balance period six weeks later; a less marked effect was seen at this time. The administration of vitamin D did not appear to affect nitrogen balance.

The patient was in positive calcium balance even on an intake of 0.27 gm. per

day (21% absorbed). When the calcium intake was increased to 0.98 gm. per day there was retention after six days of 0.57 gm. per day, or 58% of the intake. Although pancreatin added a large amount of calcium, raising the intake to 3.22 gm. per day, the patient retained 2.22 gm. per day, or 69% of the intake. The lot of pancreatin used in the second study provided less calcium, but the patient still retained 0.90 gm. per day (70% of the intake) six weeks later. Addition of vitamin D did not increase the absorption or retention of calcium; in fact, absorption decreased to

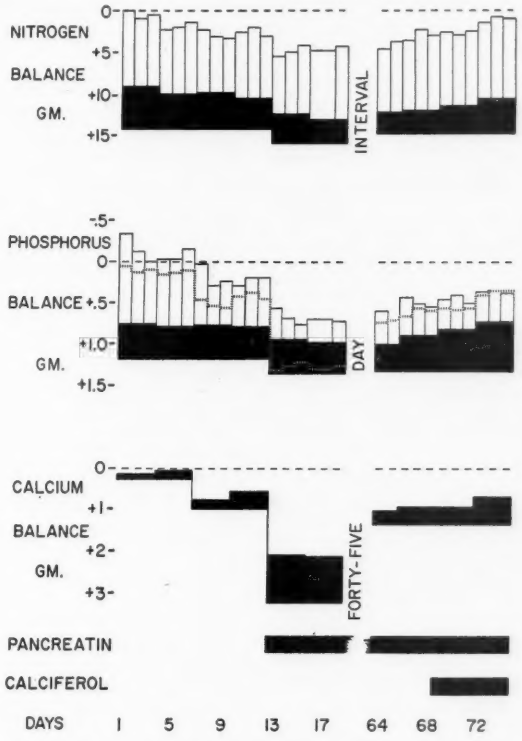

FIG. 3. Results of calcium, phosphorus and nitrogen balance study. The dotted line in the phosphorus balance figure represents the theoretic phosphorus balance.

52% of the intake. During both studies the patient put out essentially no calcium in the urine (0.02 gm. per day at most).

The phosphorus balance reflected the balances of nitrogen and calcium. The theoretic phosphorus balance was calculated from the sum of the following: nitrogen balance × 0.068 (P/N ratio of muscle) and calcium balance × 0.444 (P/Ca ratio of bone). Although the absolute values of the observed and theoretic phosphorus balances differ considerably, the changes in balance parallel each other (figure 3).

DISCUSSION

This patient presented the typical physical, x-ray and laboratory findings of hyperparathyroidism with osteitis fibrosa generalisata, caused by a para-

thyroid adenoma. Apparently this condition was completely asymptomatic: the patient's only symptom, arthritis, proved to have a different cause.

In spite of the severe bone disease there were almost no postoperative difficulties related to calcium metabolism. It took only a week for function of normal parathyroid tissue to return, as measured by return of the serum calcium to normal. The demonstration that the patient was able to retain as much as 2 gm. of calcium a day (about 0.2% of normal total body calcium) four months after removal of the tumor gives an indication of the magnitude of the previous loss of calcium, and even six months postoperatively he was retaining nearly a gram of calcium per day.

The extreme conservation of calcium after removal of the tumor is also indicated by comparison of the results of the two calcium infusion tests. Although before operation the infusion of 10 mg. per kilogram of calcium in three hours caused a rise of 1.3 mg. % in the serum calcium with the excretion in the urine of 20% of the load, postoperatively there was no rise in serum calcium, and only 9% of the load was excreted, doubtless due to the rapid deposition of calcium into bone. During both tests the serum inorganic phosphorus rose and the urine phosphorus excretion decreased. In the preoperative test the reduction of urine phosphorus could be accounted for by decreased glomerular filtration, but postoperatively the rate of tubular reabsorption of phosphorus must have increased. It is thought that when parathyroid function is normal, elevation of the serum calcium leads to diminution in parathyroid secretory activity and, therefore, to phosphorus retention.[2, 3, 4] The preoperative test is consistent with the presence of a secreting tumor, which would not be expected to be controlled by changes in the level of serum calcium. The increase in tubular reabsorption of phosphorus in the postoperative test is qualitatively the same as in normal individuals; however, the relatively large percentage increase is typical of the response found in osteomalacia.[3, 4]

The patient gave a history of an attack of acute pancreatitis and had calcification of the pancreas by x-ray. Although there was no gross steatorrhea, there was evidence of impaired pancreatic secretion. Duodenal secretions had no tryptic or amylatic activity. Stool nitrogen and fat were high, and the vitamin A tolerance test showed little rise; these disturbances were improved by administration of pancreatin. It seems likely that the elimination by the patient of 0.10 to 0.15 gm. per day of calcium in the feces when the dietary intake was 0.27 gm. per day represents a relative impairment of calcium absorption. The authors have observed fecal excretion of calcium of 0.005 gm. per day on a low calcium intake in another patient with generalized decalcification of the skeleton with apparently normal function of the gastrointestinal tract.[5] Pancreatin therapy produced a slight increase in the percentage absorption of ingested calcium, but the presence of large amounts of calcium in the pancreatin so altered the calcium intake from control to treatment periods that increased retention has little meaning. Bone repair was slow postoperatively. The serum alkaline phosphatase was still elevated six months after removal of the tumor. Since the patient was on a high calcium intake during this time, except during study programs, this delay may reflect poor calcium absorption. The histologic appearance of the bone biopsy taken a month after operation also points in this direction, for osteoclasts were still present, and osteoblastic activity was far less than might have been expected.[6]

Pancreatic insufficiency is thought to produce osteomalacia through failure to absorb vitamin D, deficiency of which causes poor absorption of calcium. Although calciferol was given to the patient while on a balance study, no effect on calcium absorption was seen. The study period was too short, however, to permit the conclusion that the patient could not absorb vitamin D normally.

It is of interest to consider the possible interrelations of the disease processes present in this patient. Chronic glomerulonephritis can produce parathyroid hyperplasia and might thus set the stage for the appearance of a parathyroid adenoma. Parathyroid hyperplasia is thought not to occur unless the renal disease causes phosphorus retention, which was not seen in this patient. There was no evidence here for the reverse process, production of renal disease by hyperparathyroidism.

The next possible cause of parathyroid hyperplasia, and thus possibly a conditioning factor in adenoma formation, is osteomalacia. Although there was no direct evidence of the presence in this patient of osteomalacia before he developed hyperparathyroidism, pancreatic insufficiency, a known cause of osteomalacia, was present. Indeed, Dent [7] has noted the coexistence of hyperparathyroidism and pancreatic disease in a number of patients. In the present case the results of the calcium infusion test performed after operation do suggest the presence of osteomalacia at that time. Albright,[8] however, has pointed out that a transient functional osteomalacia exists after removal of a parathyroid adenoma. The possibility remains that the pancreatic insufficiency in this patient did produce osteomalacia, which was followed by the appearance of the parathyroid adenoma. With preëxisting osteomalacia, hyperparathyroidism would be expected to produce severe bone disease in a short time. Under these circumstances hypercalciuria would be less marked than in a case of straightforward hyperparathyroidism, so that the formation of renal calculi would be less likely. Both of these considerations fit with this patient's course.

Lynch has recently called attention to renal disease as a complication of acute pancreatitis.[9] He believes that the lesion arises from fat embolization of the kidney, which leads, on healing, to interstitial fibrosis. One of his cases showed urinary findings suggesting glomerulonephritis. The present case may fit this category of renal disease secondary to pancreatitis, although there was also evidence for preëxisting glomerulonephritis.

The relation, if any, of gout to the other metabolic disturbances in this patient is obscure. Although hyperuricemia may be caused by nephritis, significant retention of other nitrogenous compounds is almost always present at the same time. In any case, it is doubtful if the hyperuricemia of nephritis ever produces gout.[10] Consideration of a possible relation between poor intestinal absorption and hyperuricemia brings to mind pernicious anemia, an occasional precursor of gout. This possibility was excluded. The removal of the parathyroid tumor and the period of pancreatin therapy had no effect on the gouty attacks or on the hyperuricemia.

Summary

A case is described of a 37 year old man with a history of acute pancreatitis and evidence of pancreatic insufficiency, who also developed osteitis fibrosa generalisata due to parathyroid adenoma. Evidence is presented that the hyper-

parathyroidism may have been caused indirectly by the pancreatic insufficiency. The patient also had chronic nephritis, which may have been a sequela of the acute pancreatitis, and gout.

Summario in Interlingua

Es describite le caso de un homine de 37 annos de etate con generalisate osteitis fibrose causate per un adenoma parathyroide del typo a cellulas principal. Ben que le excision del adenoma curava le anormalitates biochimic del metabolismo de calcium, le morbo ossee se curava lentissimemente. Le patiente dava un historia de un sever attacco de pancreatitis acute octo annos previemente. Il esseva constatate que ille habeva calcification del pancreas. Moderate elevationes de nitrogeno e grassia fecal indicava le presentia de un partial insufficientia pancreatic. In plus le patiente habeva ben-compensate glomerulonephritis chronic, sin retention de nitrogeno o phosphoro, que habeva essite notate primo post le attacco de pancreatitis. Un complication additional esseva le apparition durante le periodo de hospitalisation de arthritis acute que esseva diagnosticate plus tarde como gutta.

Es suggerite que le hyperparathyroidismo esseva relationate al insufficientia pancreatic in le sequente maniera: Non-absorption lipidic resultava in carentia de vitamina D con le subsequente disveloppamento de osteomalacia. Isto causava hyperplasia del parathyroides, e le hyperplasia del parathyroides preparava le campo pro le apparition de un adenoma parathyroide, analoge al apparition sporadic de un functionalmente active carcinoma del glandula thyroide in patientes con struma nodular causate per carentia de iodo.

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EDITORIAL

PROPERDIN

ALTHOUGH acquired immunity has been extensively studied and much has been learned regarding the role of the protective substances in the blood, the factors concerned with natural (spontaneous) resistance to infection are poorly understood. Recent studies, particularly by Pillemer and his associates, have demonstrated and partly characterized a previously unrecognized constituent of the serum which seems to play an important role in the defense from infection and probably in other biochemical reactions as well.

This substance, termed properdin by Pillemer,[1] was first recognized during a study of complement. In an attempt to isolate the third constituent of complement, C'3 according to the usual arbitrary nomenclature, he treated fresh normal serum with "zymosan," an insoluble purified preparation of the cell walls of yeast, consisting largely of polysaccharides of high molecular weight. This substance removed the C'3 specifically from the serum without significantly affecting the other constituents of the complement (C'1, C'2, and C'4), but the C'3 appeared to be consumed or irreversibly combined with the zymosan in the process since it could not be eluted. The eluate, however, did contain this newly recognized constituent, properdin.

The properties of properdin in vitro have been extensively studied, and it is clearly entirely distinct from immune antibodies, from complement, from all known coagulation factors, and from any previously recognized constituent of the serum although it is probably responsible for some of the activities of serum which have previously been observed.

Properdin is a euglobulin present in the electrophoretic fraction III, with a molecular weight estimated at over eight times that of gamma globulin and constituting not over 0.03% of the total serum protein. It is inactivated (in serum) at 56° but is reported to be stable up to 68° in pure solution. It withstands freezing and long storage at low temperatures but not at room temperature. It is not destroyed by trypsin, hydrazine (which removes C'4) or by antigen-antibody complexes which fix complement. Removal of divalent cations including Ca and Mg by an exchange resin inhibits its activity, but this is restored by adding Mg in physiological concentration. Free Ca seems unnecessary. Properdin also requires complement for its activity and a temperature not less than 17° C. If zymosan is added to fresh serum under these conditions, the properdin will combine with the zymosan, best at a slightly acid reaction (pH 6.9) and low ionic concentration, and the complex can be removed by centrifugalization and

[1] Pillemer, L., et al.: The properdin system and immunity. I. Demonstration and isolation of a new serum protein, properdin, and its role in immune phenomena, Science **120**: 279–285, 1954.

washed. A second extraction may be required for complete removal. Complement (C'3) will not be removed at a temperature under 20°, the extracted serum, "RP," "reagent for properdin" of Pillemer, is normal except for lack of properdin, and it can be used for the detection or titration of properdin.[2]

If the zymosan-properdin complex is digested in an alkaline (pH 7.4) buffer at a higher ionic concentration, the properdin is eluted, and it can be further purified and obtained in a concentration at least 3000 fold greater than that in the original serum, largely free from other protein. If the zymosan-serum mixture is incubated at higher temperatures, 20° to 37°, the complex will combine with the C'3 fraction of complement and remove it. The preparation and control of these reagents and their titration are laborious, technically complicated and exacting procedures and the cofactors required are labile and uncertain. In spite of this, considerable pertinent information has been accumulated.

Preparations entirely analogous to zymosan, which will combine with properdin, have been prepared from the cell walls of several species of bacteria, including *Escherichia coli, Streptococcus faecalis, Bacillus megatherium* and *Candida pulcherrina.*[3] Properdin also combines with the polysaccharides of certain types of pneumococci, with pertussis bacilli, with typhoid endotoxin, but not with diphtheria toxin. In all these reactions complement and Mg are required, and a temperature between 15° and 37°. In most instances at suitable temperatures the C'3 was also removed. The insoluble complex can be obtained by centrifugalization and properdin eluted, as from zymosan.

In many instances the bactericidal activity which fresh normal serum exerts on certain species of bacteria has been shown to be due to properdin.[4] Complement and Mg are also required. Adequately complete removal of properdin by zymosan abolishes the bactericidal activity of such serum, but this can be restored by adding properdin (from a purified preparation) unless complement has been unduly weakened by the manipulations. Much of this work has been done with the Shiga bacillus and with *E. coli,* but similar observations have been made with certain strains, only, of at least six other unrelated species, including Salmonella, Proteus, Pseudomonas, and *Bacillus subtilis.* Why other strains of these species are resistant is not known, but it is not correlated with the capacity of the cell walls to combine with properdin. The latter exerts no fungicidal effect on living cells of the strain of yeast from which zymosan was prepared. Wardlaw and Pillemer [4] have suggested that the combination may be due to a chemically specific

[2] Pillemer, L., et al.: The properdin system and immunity. III. The zymosan assay of properdin, J. Exper. Med. **103**: 1–13, 1956.

[3] Pillemer, L. et al.: The properdin system and immunity. II. Interaction of the properdin system with polysaccharides, Science **122**: 545–548, 1955.

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reaction between properdin and certain receptors of the polysaccharides in the cell wall, and if the latter is coated with antigenic envelopes of other sorts, the union may be blocked. In any case, susceptibility is a feature of the strain rather than the species. With susceptible strains, there is a fair correlation between the titer of properdin and the bactericidal activity of the serum.

Properdin may also exert an inhibitory action on certain viruses.[5] The antiviral action of fresh normal human serum in the case of Newcastle disease virus, influenza A and B and mumps was clearly demonstrated by Ginsberg and Horsfall [6] who showed that it was dependent upon thermolabile factors and not immune bodies. Wedgewood et al.[5] made a critical study of this reaction in the case of Newcastle disease virus, utilizing both inhibition of hemagglutination and reduction of the infectious activity of the virus by the serum. The activity of the fresh serum was abolished by removal of properdin, and it was restored by adding the latter from a fresh source. All fractions of complement and also Mg were necessary. The properdin activity of the mixture was reduced after inhibition of the virus although complement was not notably affected. Subsequent incubation with a cation exchange resin restored some hemagglutinating activity, presumably by removing Mg, and they suggested that the union of properdin with viruses as well as with bacterial cell walls was a stoichiometric one, and that Mg was an integral part of the complex. Many viruses, of course, are not affected by fresh normal serum.

It is quite possible that properdin may be the thermolabile factor in normal serum that neutralized variola virus (McCarthy et al.[7]), *E. coli* bacteriophage (Van Vunakis et al.), and enhanced or restored the activity of heated immune serum for vaccinia, Rous sarcoma, dengue, Western equine encephalitis, etc.[5]

Hinz et al.[8] have obtained evidence that properdin is the thermolabile factor in the serum (in addition to complement) that is responsible for hemolysis of the red cells in paroxysmal nocturnal hemoglobinuria. The conditions required for hemolysis are exactly like those necessary for the bactericidal and virucidal activities just reviewed. It has been suggested (Crosby, Dameshek) that certain clotting factors, AC globulin, thrombin, are concerned in this hemolysis. Hinz found that thrombin solutions contained considerable properdin and he believes this is the lytic agent.

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Hinz [9] has reported that properdin is required in the hemolysis of red cells that have been treated with tannic acid. It is thought that this combines with or so alters the stroma of the red cells that it becomes susceptible to the active substances—properdin plus complement—of the serum. It might be profitable to restudy some other hemolytic reactions of obscure type with reference to a possible participation of properdin.

Thus far consideration has been given only to activities of properdin in vitro. That it must play a significant role in vivo seems certain, but evidence regarding this is almost entirely indirect. The substance is present in all species so far reported, in quantities varying from 25 to 50 arbitrarily defined units per ml. in the rat, notoriously resistant to many infections, to 4 to 8 units in man and 1 to 2 units in the more susceptible guinea pig. Mice were intermediate.[1, 10] Either intravenous or intraperitoneal injection of moderate doses of zymosan or other polysaccharides of high molecular weight—bacterial cell walls, levan, dextran, gastric mucin—brings about a prompt and marked reduction of the titer of properdin in the serum, in one-half to two hours, followed in two to 14 (usually three to six) days by a rebound, often to two or three times the original level.[3] Larger doses cause a greater fall with a slower and less adequate return.

It has been shown by Rowley [11] and others that such injection in mice is followed immediately (30 minutes) by an increased susceptibility to infection with *E. coli,* so that the mice may succumb to an intraperitoneal injection of 5 organisms, of which 10,000 would be required to infect a normal mouse. After two days, resistance increased, so that the mice might withstand "several thousand" doses lethal for normal controls. This resistance could be transferred passively, but it fell to the usual level after about five days. Rats which are normally resistant succumbed to intraperitoneal infection with *E. coli,* shortly after an injection of zymosan. There is a striking parallelism, quantitatively and chronologically, between the titer of properdin in the serum (Pillemer) and the resistance of Rowley's mice to infection.

Hestrin et al.[12] had previously reported that the intravenous injection of levan, a polysaccharide of high molecular weight, increased the susceptibility of mice to intraperitoneal injection of *Salmonella typhi* within three to four hours, so that a small dose of culture which would be eliminated by a normal mouse progressively increased in the peritoneal exudate. Since no levan enters the peritoneal cavity, this susceptibility can not be due to a local action, but it was attributed to a quick interaction between the levan and the

[9] Hinz, C. F., et al.: The requirement for the properdin system in the hemolysis of human erythrocytes treated with tannic acid, J. Clin. Investigation **34**: 912, 1955 (abstract).

[10] Pillemer, L., and Ross, O. A.: Alterations in serum properdin levels following injection of zymosan, Science **121**: 732–733, 1955.

[11] Rowley, D.: Stimulation of natural immunity to *Escherichia coli* infections. Observations on mice, Lancet **1**: 232–234, 1955.

[12] Hestrin, S., et al.: Promotion of peritoneal infection by intravenous levan, Brit. J. Exper. Path. **35**: 112–117, 1954.

host, which probably restricts the flow of some antibacterial agent (properdin ?) into the peritoneal cavity.

Changes in properdin also seem to play a role in the mortality from severe posthemorrhagic shock. Fine[13] reported a careful study of dogs bled under experimental conditions which automatically, by continued bleeding or reflux of blood, kept the blood pressure at 30 mm. Hg. If the state of shock was terminated early by rapid reinfusion, recovery was the rule. If shock was maintained longer, the dogs usually died eventually in spite of additional transfusions. The fatal outcome was associated with terminal or subterminal invasion of the blood stream by intestinal bacteria which were demonstrated by blood cultures immediately post mortem in 25%. If the shock was not too protracted, by the administration of antibiotics orally or by vein, the mortality might be reduced to about 20%, but this did not protect after shock had become irreversible. Intravenous injection of doses of *E. coli* or Staphylococci which were promptly cleared by normal dogs caused progressive infection in animals in shock for more than a few hours.

Frank et al.[14] confirmed this diminution in resistance to infection in animals in posthemorrhagic shock. They found the properdin (in dogs) was reduced, usually within two hours, and this was not replenished by late transfusions. Complement was but little affected.

Pillemer et al.[10] also have reported that injections of zymosan into mice and rats, which reduce the properdin in the serum, markedly increase their susceptibility to total body irradiation. In these various manipulations there was often a strikingly clear relationship between the titer of properdin in the serum and the susceptibility of the subjects to infection.

The possibility of utilizing properdin therapeutically in such situations naturally comes to mind, although there is thus far no direct experimental evidence to demonstrate its value in this respect. The lability of the material except at low temperatures would offer serious practical difficulties to its commercial exploitation. Methods for concentrating the material appear relatively simple, but the yield from human serum would probably be too low to make this source feasible commercially. The use of properdin of other origin involves the usual difficulties inherent in the administration of foreign sera. That properdin is antigenic is shown by the recent report of Pillemer et al.[15] of the production of a specific antiserum in rabbits by injections of the partly purified material from human serum. By treating this antiproperdin serum with human serum freed from properdin, "RP," the activity toward other protein factors was eliminated. The resulting extracted antiserum no longer formed a visible precipitate or fixed complement

[13] Fine, J.: Relation of bacteria to the failure of blood volume therapy in traumatic shock, New England J. Med. **250**: 889–895, 1954.

[14] Frank, E., et al.: Serum properdin levels in hemorrhagic shock, Proc. Soc. Exper. Biol. and Med. **89**: 223–225, 1955.

[15] Pillemer, L., et al.: Preparation and properties of antihuman properdin rabbit serum, Science **125**: 1244–1245, 1957.

when mixed with human serum, but it did specifically inactivate properdin, both of human origin and more or less completely that from other species. It seems likely, therefore, that the usefulness of heterologous properdin, if any, may be limited to the interval required for the development of specific antibodies to it and presumably also of disturbing hypersensitiveness as well.

Obviously much more work will be required to determine whether properdin has any practical therapeutic value. Although much of the evidence is indirect, there is little doubt that properdin plays a significant nonspecific role in the defense against infection and that it is an important factor in natural immunity. For these reasons alone it merits further careful study.

PAUL W. CLOUGH

REVIEWS

Clinical Cardiopulmonary Physiology. Edited by BURGESS L. GORDON, M.D. Sponsored by the American College of Chest Physicians. 759 pages; 18 × 26 cm. Grune & Stratton, New York. 1957. Price, $15.75.

The first word of the title establishes the theme of the book. A tremendous volume of work in basic cardiac and pulmonary physiology together with clinical applications of the derived knowledge has been accomplished and recorded in the current scientific and medical literature in the past ten years.

As is so frequently true in medicine the work is done by men who have devoted their major interest to it. There is a wide gap between them and the men who must apply the results of their work to clinical situations, which gap must be bridged by communication, interpretation, and explanation.

This is the purpose of the book, and it is admirably accomplished. It is not written for the physiologist or the physician-physiologist. Indeed a good portion of it must seem very elementary to the physiologic savant or the pundit in pulmonary diseases.

Physiologic methods and rationale, normal and abnormal values, and the functional effect with its clinical consequences in a wide variety of diseases of the heart and lungs are presented by men of special experience and authority in the field of cardiopulmonary disease.

The book is recommended to all who deal with clinical problems presented by diseases of the chest.

PATRICK B. STOREY, M.D.

Borderlands of the Normal and Early Pathologic in Skeletal Roentgenology. 10th Ed. By ALBAN KÖHLER, revised by E. A. ZIMMER, English translation arranged and edited by JAMES T. CASE, M.D., D.M.R.E. (Cambridge), Professor Emeritus of Radiology, Northwestern University Medical School, Chicago; Director, Memorial Cancer Foundation, Santa Barbara, California. 723 pages; 17 × 26.5 cm. Grune and Stratton, New York. 1956. Price, $24.50.

Borderlands of the Normal and Early Pathologic in Skeletal Roentgenology is an outstanding reference on the skeletal system. It presents a wealth of roentgenologic information concerning the borderlines of normal and the beginning of pathologic alterations in the skeletal system.

The text is divided into six sections: (1) General fundamental considerations, (2) upper extremity, (3) shoulder girdle; soft tissues of the thorax and the cervical region, (4) the cranial skeleton, (5) the spinal column and the pelvis and (6) the lower extremity. The normal variants and early pathologic changes of each bone are considered individually.

The book is translated in such a fashion as to be easily read and understood. It is extremely well illustrated, mainly with roentgenograms but also with a few photographs and sketches. The bibliography at the end of each section is extensive and up-to-date. In fact, the bibliography in this English version is more extensive than the one in the tenth German edition.

This book is one of the most important ever published on roentgenology of the skeletal system. While it is not one that will be read in its entirety, it is an outstanding reference for all roentgenologists, orthopedists and pathologists.

JOHN M. DENNIS, M.D.

Atlas d'Électrocardiographie, avec des Notions de Vectocardiographie a l'Usage du Médecin Praticien et de l'Étudiant. 4th Ed. By V. FATTORUSSO and O. RITTER. 295 pages; 25 × 17.5 cm. Masson et Cie., Paris. 1956. Price, 3.200 fr.

This is the fourth edition of this textbook on electrocardiography. The book is divided into six parts: the normal electrocardiogram, the variations in the forms of the ventricular complex, alterations of rhythm, electrocardiographic syndromes, electrophysiology and a section on vectorcardiography. The text is well organized, and the 231 illustrations are particularly valuable. The illustrations are fully described and consist of excellent diagrams as well as a good selection of electrocardiograms.

This book is much more than an atlas as the title implies, since the text is sufficiently comprehensive. The section on arrhythmias is especially to be commended. Although there are numerous texts on electrocardiography which are readily available, this text should be a valuable asset to the cardiologist, practicing physician, and student as one of the more highly recommended textbooks on electrocardiography.

L. S.

Symposium on Myasthenia Gravis. Guest Editors: HENRY R. VIETS, M.D., and GEORGE D. GAMMON, M.D. 88 pages; 27 × 19.5 pages (paper-bound). Reprinted from Vol. 19, Nov. 1955, *The American Journal of Medicine;* distributed by The Myasthenia Gravis Foundation, Inc., New York. 1955. Limited number of reprints still available, on request.

This is a reprint of papers read at the First International Conference on Myasthenia Gravis. The volume is 745 pages and includes eighteen papers ranging from a presentation of the problems of myasthenia gravis to the modern treatment and management of patients with this disease. The physiology and pharmacology of normal and myasthenic muscles and neuromuscular transmission is discussed in several papers. The relation of the thymus to myasthenia is also considered.

This volume is an interesting and informative presentation of the current status of this disease.

C. V. B.

The Practice of Dynamic Psychiatry. By JULES H. MASSERMAN, M.D. 790 pages; 24 × 16 cm. W. B. Saunders Co., Philadelphia. 1955. Price, $12.00.

Part I of *The Practice of Dynamic Psychiatry* is given over to investigation of the rationale, objectives, and methods of the psychiatric interview, together with discussion of many of the pitfalls and mistakes often encountered therein. It includes much information on psychiatric history taking, and essentials and meaning of the mental status examination.

In Part II, the various types of psychiatric illness are discussed—neuroses, personality pattern disturbances, psycho-physiologic dysfunctions (fugue states, conversion reactions, etc.), mental deficiency, and the psychotic disorders. There are many illuminating, well-reported and selected case histories scattered through this section, as, in fact, there are through the whole book.

The major part of the work, Part V, is concerned with clinical psychotherapy. The origin in hypnotic suggestion of Freud's early ideas is described, and the later development of his main ideas. The more important current schools of analytic psychotherapy, deviant from, but derived from Freudian analysis, are described, and the differences between them examined. The greater part of this section is not devoted to strict psychoanalytic therapy, but to briefer and more direct forms of psychotherapy, based on psychoanalytical concepts. A great deal of very practical helpful information is offered on specific problems met by the therapist, in many varying situations.

S. E. B.

Gynecologic Cancer. 2nd Ed. By JAMES A. CORSCADEN, Ph.B., M.D. 546 pages; 15.5 × 23.5 cm. The Williams and Wilkins Company, Baltimore. 1956. Price, $10.00.

The second edition of Dr. Corscaden's *Gynecologic Cancer* is a timely, authoritative and complete presentation of the problem. As with the first edition, this is a concise, understandable, well-written book with a really representative bibliography. The present edition brings up to date the ever changing picture of gynecologic cancer, a large assignment, but very well done. This text, stressing early diagnosis, careful conservative therapy and meticulous follow-up management, is a worthwhile addition to the working library of everyone whose practice includes women.

W. K. D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Antikoagulantien. Ihre Bedeutung für die angewandte Gerinnungsphysiologie, Pathologie und Klinik thromboembolischer Erkrankungen. By PROFESSOR DR. MED. HABIL. EBERHARD PERLICK, Oberarzt der Med. Klinik der Medizinischen Akademie, Magdeburg (with introduction by PROFESSOR ROLF EMMRICH, Direktor of the Klinik). 290 pages; 24.5 × 17.5 cm. 1957. Georg Thieme Verlag, Leipzig. Price, Gebunden DM 36.—

The Blood Pressure in a Population: Blood Pressure Readings and Height and Weight Determinations in the Adult Population of the City of Bergen. Acta Medica Scandinavica *Supplementum CCCXXI.* By JOHS. BØE, M.D., SIGURD HUMERFELT, M.D., and FRØYSTEIN WEDERVANG, CAND. OECON. 336 pages; 24 × 18 cm. (paper-bound). 1957. A. S. John Griegs Boktrykkeri, Bergen, Norway. Sent out as a supplement to *Acta Medica Scandinavica.* A limited number of reprints available without cost from Universitetet I Bergen, Bergen, Norway.

The Chemistry and Biology of Purines. Ciba Foundation Symposium. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and CECILIA M. O'CONNOR, B.Sc. 327 pages; 21 × 14 cm. 1957. Little, Brown and Company, Boston. Price, $9.00.

Clinical Proctology. 2nd Ed. By J. PEERMAN NESSELROD, B.S., M.S., M.Sc. (Med.), M.D., F.A.C.S., F.A.P.S., Assistant Professor of Surgery, Northwestern University Medical School, etc. 296 pages; 24.5 × 15.5 cm. 1957. W. B. Saunders Company, Philadelphia. Price, $7.00.

Collected Papers of The Mayo Clinic and The Mayo Foundation. Vol. XLVIII, 1956. Edited by RICHARD M. HEWITT, B.A., M.A., M.D., JOHN R. MINER, B.A., Sc.D., JAMES R. ECKMAN, A.B., M.A., Ph.D., M. KATHARINE SMITH, B.A., CARL M. GAMBILL, A.B., M.D., M.P.H., FLORENCE L. SCHMIDT, B.S.E., GEORGE G. STILWELL, A.B., M.D., and GUY WHITEHEAD, B.A., M.A., Ph.D. 778 pages; 24 × 15.5 cm. 1957. W. B. Saunders Company, Philadelphia. Price, $12.50.

Differentialdiagnose innerer Krankheiten. By PROF. DR. ROBERT HEGGLIN. 749 pages; 25 × 17.5 cm. 1957. Georg Thieme Verlag, Stuttgart; in the U.S.A. and Canada: Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 79.50.

The Electrocardiogram: Its Interpretation and Clinical Application. 2nd Ed. By LOUIS H. SIGLER, M.D., F.A.C.P., F.C.C.P., F.A.C.C., Attending Cardiologist and Chief of Cardiac Clinics, Coney Island Hospital, etc. 312 pages; 24 × 15.5 cm. 1957. Grune & Stratton, New York. Price, $8.75.

Fluid and Electrolytes in Practice. 2nd Ed. By HARRY STATLAND, M.D., Associate in Medicine, University of Kansas School of Medicine, etc. 229 pages; 23.5 × 15.5 cm. 1957. J. B. Lippincott Company, Philadelphia. Price, $6.00.

Goepp's Medical State Board Questions and Answers. 9th Ed. By HARRISON F. FLIPPIN, M.D., Professor of Clinical Microbiology, The Graduate School of Medicine, The University of Pennsylvania. Editorial Consultants: WILLIAM S. BLAKEMORE, M.D., Assistant Professor in Surgery, The School of Medicine, The University of Pennsylvania; JEFFERSON H. CLARK, M.D., Associate in Pathology, The Graduate School of Medicine, The University of Pennsylvania; GEORGE M. EISENBERG, D.Sc., Associate in Microbiology, The Graduate School of Medicine, The University of Pennsylvania; and GEORGE L. HOFFMAN, M.D., Associate Professor in Obstetrics and Gynecology, The School of Medicine, The University of Pennsylvania. 569 pages; 24.5 × 16 cm. 1957. W. B. Saunders Company, Philadelphia. Price, $8.00.

Gout. By JOHN H. TALBOTT, A.B., M.D., D.Sc. (Hon.), Professor of Medicine, University of Buffalo School of Medicine, etc. 205 pages; 22.5 × 14.5 cm. 1957. Grune & Stratton, New York. Price, $6.75.

William Harvey: His Life and Times: His Discoveries: His Methods. By LOUIS CHAUVOIS; foreword by SIR ZACHARY COPE. 271 pages; 24 × 15.5 cm. 1957. Philosophical Library, New York. Price, $7.50.

Health and Medical Care in New York City: A Report by The Committee for the Special Research Project in the Health Insurance Plan of Greater New York. 275 pages; 28 × 20 cm. 1957. Published for the Commonwealth Fund by Harvard University Press, Cambridge. Price, $7.50.

J. A. M. A. Clinical Abstracts of Diagnosis and Treatment, Published with the Approval of the Board of Trustees, American Medical Association. 564 pages; 22.5 × 14 cm. 1957. Intercontinental Medical Book Corporation with Grune & Stratton, Inc., New York. Price, $5.50.

Management of the Patient with Headache. By PERRY S. MACNEAL, M.D., F.A.C.P., Physician to Pennsylvania Hospital and Benjamin Franklin Clinic, Philadelphia, etc.; BERNARD J. ALPERS, M.D., Sc.D. (Med.), F.A.C.P., Professor and Head of the Department of Neurology, Jefferson Medical College, etc.; and WILLIAM R. O'BRIEN, M.D., F.A.P.A., Psychiatrist and Head of the Department of Psychiatry, Pennsylvania Hospital, etc. 145 pages; 20.5 × 13.5 cm. 1957. Lea & Febiger, Philadelphia. Price, $3.50.

A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology. 8th Ed. By TORALD SOLLMANN, M.D., Professor Emeritus of Pharmacology and Materia Medica, School of Medicine, Western Reserve University, Cleveland, Ohio. 1,535 pages; 26 × 18 cm. 1957. W. B. Saunders Company, Philadelphia. Price, $20.00.

Meprobamate and Other Agents Used in Mental Disturbances. (Annals of The New York Academy of Sciences, *Vol. 67, Art. 10, pages 671–894.*) JAMES G. MILLER and FRANK M. BERGER (Conference Co-chairmen), L. ALEXANDER, H. W. BAIRD, H. BECKMAN, W. H. BOWER, H. A. DICKEL, H. H. DIXON, N. M. DIXON, A. DORA, S. B. EISEN, S. H. EISENBERG, H. ELKINS, A. P. FRIEDMAN, R. W. GERARD, H. E. GILLETTE, L. A. GREENBERG, R. GREENHOUSE, E. H. HESS, E. G. HILER, L. E. HOLLISTER, H. F. HUNT, A. HUXLEY, E. H. JENNEY, E. L. KELLY, T. A. LAMPHIER, D. LESTER, H. R. LITCHFIELD, D. G. MARQUIS, J. S. NEVIASER, W. A. OSINSKI, C. C. PFEIFFER, A. RAPOPORT, A. J. RIOPELLE, J. ROSENFELD, M. SABSHIN, R. ST. PIERRE, E. B. SCHLESINGER, R. P. SMITH, R. T. SMITH, E. A. SPIEGEL, E. G. SZEKELY, H. L. WILLIAMS, J. A. WOOD and T. H.

WYCIS. 224 pages; 23 × 15 cm. (paper-bound). 1957. The New York Academy of Sciences, New York. Price, $4.08.

Obesity: Its Cause, Classification, and Care. By E. PHILIP GELVIN, M.D., F.A.C.P., Associate in Medicine, New York Medical College, Flower and Fifth Avenue Hospital, etc.; and THOMAS H. MCGAVACK, M.D., F.A.C.P., Professor of Clinical Medicine, New York Medical College, Flower and Fifth Avenue Hospital, New York. 146 pages; 21 × 14 cm. 1957. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $3.50.

Orthopedic Surgery in the Mediterranean Theater of Operations. Surgery in World War II. Medical Department, United States Army. Editor in Chief: COLONEL JOHN BOYD COATES, JR., MC; Editor for Orthopedic Surgery: MATHER CLEVELAND, M.D.; Associate Editor: ELIZABETH M. MCFETRIDGE, M.A. 368 pages; 26 × 17.5 cm. 1957. Office of the Surgeon General, Department of the Army, Washington, D. C. Price, $4.00 (Buckram); for sale by the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C.

Peripheral Circulation in Health and Disease. By WALTER REDISCH, M.D., F.A.C.P., Associate Professor of Clinical Medicine, New York University College of Medicine; and FRANCISCO F. TANGCO, M.D., B.S., Assistant Professor of Medicine, University of the Philippines Medical School, Manila, P. I., etc.; with a special section by R. L. DEC. H. SAUNDERS, M.D., F.R.S.E., Professor and Head of the Department of Anatomy, Dalhousie University Medical School, Halifax, Nova Scotia, Canada; and Associates. 154 pages; 26 × 18 cm. 1957. Grune & Stratton, New York. Price, $7.75.

Practitioners' Conferences Held at The New York Hospital-Cornell Medical Center. Vol. 6. Edited by CLAUDE E. FORKNER, M.D., F.A.C.P., Professor of Clinical Medicine, Cornell University Medical College, etc. 378 pages; 22 × 14.5 cm. 1957. Appleton-Century-Crofts, Inc., New York. Price, $6.75.

Recent Advances in Anaesthesia and Analgesia (Including Oxygen Therapy). 8th Ed. By C. LANGTON HEWER, M.B., B.S. (Lond.), M.R.C.P. (Lond.), F.F.A.-R.C.S. (Eng.), Anesthetist in charge of Department, St. Bartholomew's Hospital, etc.; and J. ALFRED LEE, M.R.C.S., L.R.C.P., M.M.S.A., F.F.A.R.C.S. (Eng.), Consultant Anaesthetist to the Southend-on-Sea Hospital, etc. 295 pages; 21 × 14 cm. 1957. Little, Brown and Company, Boston. Price, $8.50.

Regulation and Mode of Action of Thyroid Hormones. Ciba Foundation Colloquia on Endocrinology. Vol. 10. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch.; and ELAINE C. P. MILLAR, A.H.-W.C., A.R.I.C. 311 pages; 21 × 14 cm. 1957. Little, Brown and Company, Boston. Price, $8.50.

Rendiconti Istituto Superiore di Sanità. English Edition: Special Number on Pilot Plant Techniques of Submerged Fermentation. Vol. XVII. 251 pages; 24 × 17 cm. (paper-bound). 1954. Fondazione Emanuele Paterno, Rome. Price, Lit. 5.000.

Scoville's The Art of Compounding. 9th Ed. By GLENN L. JENKINS, Dean and Professor of Pharmaceutical Chemistry, Purdue University School of Pharmacy, Lafayette, Indiana; DON E. FRANCKE, Chief Pharmacist, University Hospital, University of Michigan, Ann Arbor, Michigan; EDWARD A. BRECHT, Dean and Professor of Pharmacy, University of North Carolina, School of Pharmacy, Chapel Hill, North Carolina; and GLEN J. SPERANDIO, Associate Professor of Pharmacy, Purdue University School of Pharmacy, Lafayette, Indiana. 551 pages; 26 × 18.5 cm. 1957. The Blakiston Division, McGraw-Hill Book Company, Inc., New York. Price, $11.00.

The Specialties in General Practice. 2nd Ed. Edited by RUSSELL L. CECIL, M.D., Professor of Clinical Medicine, Emeritus, Cornell University Medical College, New York City; and HOWARD F. CONN, M.D., Fellow, Department of Physiology, Baylor University College of Medicine and the Blue Bird Clinic, Methodist Hospital, Houston, Texas. 780 pages; 26 × 18 cm. 1957. W. B. Saunders Company, Philadelphia. Price, $16.00.

Study Group on Atherosclerosis and Ischaemic Heart Disease: Report. World Health Organization Technical Report Series No. 117. 40 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Study Group on the Ecology of Intermediate Snail Hosts of Bilharziasis: Report. World Health Organization Technical Report Series No. 120. 38 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Systemic Arterial Embolism: Pathogenesis and Prophylaxis. Modern Medical Monographs 14. By JOHN MARTIN ASKEY, M.D., Associate Clinical Professor of Medicine, University of Southern California School of Medicine. 157 pages; 22.5 × 14.5 cm. 1957. Grune & Stratton, New York. Price, $5.75.

Tumors of the Eye and Adnexa (Atlas of Tumor Pathology, Section X, Fascicle 38). By ALGERNON B. REESE, M.D., Attending Surgeon and Pathologist, Institute of Ophthalmology, New York City, etc. 205 pages; 26 × 20 cm. (paper-bound). 1956. Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the Division of Medical Sciences of the National Academy of Sciences—National Research Council, Washington, D. C. For sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington, D. C., at $2.00.

Tumors of the Kidney, Renal Pelvis and Ureter (Atlas of Tumor Pathology, Section VIII, Fascicle 30). By BALDUIN LUCKÉ, M.D., Dr. P. H., Late Professor of Pathology, University of Pennsylvania, Philadelphia, Pennsylvania; and HANS G. SCHLUMBERGER, M.D., Professor of Pathology, Ohio State University, Columbus, Ohio. 208 pages; 26 × 20 cm. (paper-bound). 1957. Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the Division of Medical Sciences of the National Academy of Sciences—National Research Council, Washington, D. C. For sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington, D. C., at $2.25.

Tumors of the Pituitary Gland and Infundibulum (Atlas of Tumor Pathology, Section X, Fascicle 36). By JAMES W. KERNOHAN, M.D., Chairman, Sections of Pathologic Anatomy and Surgical Pathology, Mayo Clinic, Rochester, Minnesota, etc.; and GEORGE P. SAYRE, M.D., Section of Pathologic Anatomy, Mayo Clinic, Rochester, Minnesota, etc. 81 pages; 26 × 20 cm. (paper-bound). 1956. Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the Division of Medical Sciences of the National Academy of Sciences—National Research Council, Washington, D. C. For sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington, D. C., at $1.00.

Der ultramikroskopische Bau von Herz und Kapillaren. By DR. BRUNO KISCH. 109 pages; 23.5 × 15.5 cm. (paper-bound). 1957. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, brosch DM 22.—; geb. DM 25.—